Misoprostol and its effect on the resistance indices of uterine arteries and the fetal heart rate in early pregnancy

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Preface

Abstract

In 1985, prostaglandins of the E and F series have been found to have effects on the contractility of the uterine arteries (UAs) and its branches in vitro (Maigaard S et al., 1985). The prostaglandin E_1 analogue, gemeprost has been studied by Joupplia P et al. in 1994. The impact of gemeprost on the uterine artery (UA) and the fetal heart rate (FHR) during the first trimester pregnancy were studied. They found that vaginal application of gemeprost in early pregnancy increases the vascular resistance of UAs and the effect is not affected by parity or gestation and the change is similar in both UAs. Otherwise some investigators have reported that gemeprost increases the median value of pulsatility index in the dominant uterine artery in the first trimester and can induce fetal bradycardia and sometimes demise (Valentin L et al., 1995).

Misoprostol is a prostaglandin E_1 analogue which was originally developed as a prophylactic agent against peptic ulceration in patients taking non steroidal anti-inflammatory drugs (NSAID). Misoprostol has been used in Obstetrics and Gynecology (O&G) since the late 1980s. It has been used as an abortifacient agent in first trimester (Baird DT et al., 1992) and second trimester (Bugalho A et al., 1993) with or without mifepristone. More recently, its use in late pregnancy to induce labour has been reported (Margulies M et al., 1992).

As misoprostol is as effective as gemeprost and is more convenient to use, it has been a substitute for gemeprost in therapeutic abortion. Misoprostol is also

being used in the second and third trimesters of pregnancy where fetal compromise is a potential hazard. However, there has been little research into the effect of misoprostol on the utero-placental circulation and its potential impact on the fetus.

The aim of this thesis was to assess the effects of misoprostol on the resistance of the main uterine arteries and on the fetus in normal early pregnancy. This thesis tests the following hypotheses:

Hypothesis 1

That misoprostol (200μg) increases the resistance of the main uterine arteries in normal early pregnancy.

Result

Misoprostol significantly increased the resistance indices including pulsatility index (PI) and systolic velocity to diastolic velocity ratio (S/D ratio) of the main uterine arteries (both $P<0.01$). The change was not affected by the presence of abdominal pain.

Conclusion:

Oral misoprostol increases the vascular resistance of uterine arteries in early pregnancy.

Hypothesis 2

An oral dose of 200μg of misoprostol affects the fetal heart rate (FHR) in early pregnancy.

Result

FHR did not significantly change after oral misoprostol ($P>0.05$). All fetuses were alive at the second ultrasound examination.

Conclusion

A single oral dose of 200μg misoprostol does not appear to cause terminal fetal compromise in early pregnancy.

米索前列醇對早孕子宮動脈阻力指數和胎心率的影響

摘要

研究目的：探討米索前列醇對早期妊娠子宮動脈的阻力和對胎兒的影響。研究方法：對四十例孕齡 7-15 周的正常婦女每人給予 200μg 米索前列醇，服藥前及服藥后約 1 小時均進行陰道超聲檢查，測量其子宮動脈的搏動指數（ PI ），收縮與舒張血流速度的比值（ S/D 比值）和胎心率（ FHR ）。 結果表明：米索前列醇能顯著增加子宮動脈的阻力指數包括 PI 和 S/D 比值（兩者 P 均 <0.01 ），且此改變不被藥物引起的腹痛所影響。 另外，口服 200μg 米索前列醇約 1 小時沒有顯著影響胎心率（ $P>0.05$ ）。 研究提示：早孕期單劑量 200μg 米索前列醇在 1 小時內可令子宮動脈的阻力增加但不影響胎心率。 米索前列醇如用于晚期引產其間應對胎兒密切監護，而其安全性仍有待研究。

Statement of Work

The work contained in this thesis was performed at the Prince of Wales Hospital, Sha Tin, New Territory, Hong Kong between 20 May 1996 to 22 April 1997. I was an M. Phil student of the Chinese University of Hong Kong from September 1995 to June 1997.

All the work presented in this thesis is my own work and was performed under the supervision of Professor Tony Chung, Kwok-Hung, Associate Professor, Department of Obstetrics and Gynaecology, the Chinese University of Hong Kong.

None of this word has been submitted to any other university of institute for degree of diploma.

Tse On Ki

Dedication and Acknowledgements

This thesis is dedicated to my dear parents.

I wish to express my sincere gratitude to my supervisor, Professor Tony Chung, for guiding me on this project, for his constant encouragement and help in all possible ways over the years. I also thank Professor Allen Chang MZ for his advice and support, in the Department of Obstetrics & Gynaecology, the Chinese University of Hong Kong.

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LIST OF ABBREVIATIONS

AA	Arachidonic acid
AC	Abdomen Circumference
AP	Anterior - Posterior
BPD	Biparietal Diameter
bpm	Beats Per Minute
CD	Coloured Doppler
CI	Confidence Interval
CRL	Crown Rump Length
CWD	Continuous Waves Doppler
Cmax	Maximum Concentration
CNS	Central Nerve System
ECG	Electrocardiogram
FHR	Fetal Heart Rate
FL	Femur Length
IV	Intravenous
LS/D	Systolic to Diastolic ratio of Left Uterine Artery
LD_{50}	Median Lethal Dose
LPI	Pulsatility Index of Left Uterine Artery
MHz	Megahertz, Million Cycles Per Second
NSAID	Non-Steroidal Anti-Inflammatory Drugs

O & G	Obstetrics and Gynaecology
PGs	Prostaglandins
PGE	Prostaglandin E
PI	Pulsatility Index
PWD	Pulsed Waves Doppler
RS/D	Right S/D ratio
RI	Resistance Index
RIA	Radio-immunoassay
RPI	Right Pulsatility Index
ROM	Rupture of Membrane
SD	Standard Deviation
SEM	Standard Error Mean
S & C	Suction and Curettage
S/D ratio	Systolic Velocity to Diastolic Velocity ratio
TAS	Transabdominal Sonography
TVS	Transvaginal Sonography
TOP	Termination of Pregnancy
$t_{1/2}$	Half-Life of Drug
UA	Uterine Artery
UAs	Uterine Arteries
UA-S/D	Uterine-Artery S/D ratio
UA-PI	Uterine-Artery Pulsatility Index

Chapter 1

Introduction

1. Introduction to thesis

This chapter presents an overview of the thesis. In addition, it introduces misoprostol and another commonly used prostaglandin analogue -gemeprost and discusses their use in Obstetrics & Gynaecology, especially current use of misoprostol for induction of labour with where there is a viable pregnancy and the implications for safety.

1.1 Misoprostol

1.1.1 Description and History of Drug

Misoprostol is a prostaglandin E_1 analogue. It was originally developed as a prophylactic against gastric and duodenal ulcers caused by aspirin and non-steroidal anti-inflammatory drugs (NSAID). This is because misoprostol can decrease gastric acid secretory and inhibit endogenous histamine release (Walt RP, 1990). It also has mucosal cytoprotective effects (Anon, 1988).

Misoprostol has a short elimination half time and relatively long duration of action, which is 21-35 minutes and 24 hours respectively. It is orally active and is easy to store. Furthermore, it costs less than another PGE_1 analogue-gemeprost. The details of pharmacology, pharmacokinetics and will be further discussed in chapter 3.3.

1.1.2 Current Use in Obstetrics and Gynaecology

The potent uterotonic action of misoprostol, which was once an unwanted side effect, has become a new application of misoprostol in O & G in recent years. A brief review is shown below. Further discussion of the research shall be presented in chapter 3.

1.1.2.1 Termination of Pregnancy (TOP)

Misoprostol has been used in TOP alone and combination with methotrexate in first trimester (Creinin MD, Vittinghoff E, 1994). Misoprostol also has been used for abortion with mifepristone (RU 486) orally or vaginally in first trimester (el-Refaey H et al.,1995). Vaginal administration of misoprostol was more effective and better tolerated than oral administration for the induction of first-trimester abortion after the administration of mifepristone. Misoprostol, given alone, has been reported in TOP in second trimester (Jain JK, Mishell DR Jr, 1994). Misoprostol combined with mifepristone for TOP in second trimester has also conducted by el-Refaey H et al. (el-Refaey H, Templeton A, 1995). A study has compared the efficacy of misoprostol with gemeprost in second trimester TOP (el-Refaey H et al., 1993). There was no significant difference in the outcomes between the two groups.

1.1.2.2 Cervix Priming prior to Surgical Treatment of Pregnancy Failure

Cervical laceration is a known complication of surgical evacuation of the uterus in TOP. Priming with misoprostol to soften and dilate the cervix can reduce mechanical force required and hence reduce the chance of trauma (el-Refaey et al., 1994). Edwards D et al. (1995) have studied 595 patients who were given misoprostol orally 30 to 60 minutes before surgical TOP. They reported that this facilitated the TOP. A 100μg dose of misoprostol was given to induce of labour in women with late fetal death (Bugalho A et al., 1995). Successful induction was achieved in 81% with an induction-to-delivery interval of 13.8 hours. The authors noted few side effects apart from diarrhoea.

1.1.2.3 Medical management of spontaneous abortion

The current standard management for spontaneous abortion is surgical evacuation. However, in recent years, a number of studies have been shown that misoprostol can be effective in evacuating a proportion of uteruses where there are retained products of gestation (Chung T et al., 1994).

1.2 Gemeprost

Gemeprost, also known as cervagem and ONO-802, is 16,16-dimethyl-trans-Δ^2-prostaglandin E_1 methyl ester. Its chemical formula is $C_{23}H_{38}O_5$. It is

presented as a suppository and can be administered both by vaginal and intrauterine routes. Each suppository contains 1mg gemeprost.

Gemeprost is used for softening and dilatation of cervix before transcervical intrauterine operative procedures in pregnancies in the first and second trimester of gestation. In this condition, one suppository is inserted into the posterior vaginal fornix three hours before surgery. It is also used for therapeutic TOP in the first and second trimester (Cameron IT, Baird DT, 1984).

1.3 Doppler Sonography and Assessment of Blood Velocity

It is now possible to use Doppler sonography to study the flow velocity of most blood vessels in the human body. The uterine arteries are relatively accessible by both transabdominal and transvaginal sonography. In pregnancy, these vessels are relatively easily identified and measuring the flow velocities through the vessels can make an assessment of the resistance in the utero-placental. This will be further discussed in chapter 4.

1.4 Overview of Thesis

In recent years, misoprostol, which has been shown to have potent uterotonic actions comparable to gemeprost, has been increasingly used to induce labour in the third trimester of pregnancy where there is a viable fetus and where

the birth of a normal healthy baby was expected (Margulies M et al., 1992). It has been shown that misoprostol has similar actions in the first trimester as gemeprost. However, gemeprost is contraindicated in the third trimester because of the threat they pose for the fetus because they cause tetanic uterine contractions.

In addition, misoprostol has been used for cervical priming in pre-labour rupture of membranes (ROM) at term (Ngai SW et al., 1996). The perinatal outcome were similar in the misoprostol group and placebo group. So the investigators concluded that misoprostol at a dose of 200μg is effective for cervical priming in patients with pre-labour ROM at term. These results were consistent with those of Marguiles et al. (1992).

There have been two studies that have examined the impact of gemeprost on the pulsatility index of uterine arteries during the first trimester pregnancy. The first study found that vaginal application of gemeprost in early pregnancy increases the vascular resistance of uterine arteries and the effect is not affected by parity or gestational age and the change is similar in both uterine arteries (Joupplia P, Suomalainen-KÖnig S, 1994). The authors recruited 21 patients and found that the mean value of pulsatility index increased significantly from 2.01(±0.53) to 3.47(±0.85) before and after drug administration ($p<0.001$). Another group of investigators studied 67 pregnant individuals and found that gemeprost significantly increased the median value (from 2.4 to 8.5, $P<0.01$) of pulsatility index in the arteries of utero-placental circulation (including dominant uterine

arteries and subchorionic arteries, the intrachorionic area and arteries in the wall of the corpus luteum) in the first trimester and can induce fetal bradycardia (130 vs. 163 bpm, p=0.003) and sometimes causes demise (Valentin L et al., 1995). Unlike the former study, Valentin et al. also studied the fetal heart rate, which reflects the well-being of fetus. Both studies reached broadly similar conclusions. Gemeprost can increase pulsatility index of uterine arteries (UA-PI) in first trimester pregnancy. This may reflect that gemeprost may decrease uterine perfusion resulting in impaired oxygenation of the fetus, in turn causing fetal heart rate to low down and even fetal death.

Misoprostol, like gemeprost, is a PGE_1 analogue. Potentially it may have the same adverse effects on the fetus. However, up to now, to the candidate's knowledge, there has been no published studies examining the impact of misoprostol on blood flow velocity of the uterine vessels. Compared with gemeprost, with its plasma elimination half-life is about 3-4 hours, the half life of misoprostol is shorter and it is also active orally. Whilst there are obvious advantages in introducing misoprostol for clinical use, the candidate notes that its use in late pregnancy, in the form of clinical trials, has not been preceded by appropriate investigation of its effect on the fetus and the utero-placental circulation. This is of relevance since the use of misoprostol in late pregnancy, for example to induce labour, may be potentially dangerous to the fetus.

1.5 Aim of this Study

Misoprostol has been advocated to induce labour in clinical Obstetrics for several years. However there has not been adequate research on its effect on the fetus and uteroplacental circulation. This study assesses the effects of misoprostol on the uteroplacental circulation in early human pregnancies.

Chapter 2

2. Physiological and Anatomical Features of Pregnancy

During pregnancy, there are exceptional changes in the cardiovascular system to meet the demands of the enlarging uterus, the growing fetus and physical variation of the mother. This chapter briefly describes the changes that occur in the blood, the changes of the cardiovascular dynamics and the changes on the regional distribution of blood flow in uterus. Then it focuses on the blood supply to the uterus. The changes of pelvic anatomy is also important to our study, it may be described with transvaginal sonography as a reference.

2.1 Cardiovascular System Changes in Pregnancy

2.1.1 Changes in the Blood

The blood changes will be considered in blood volume, plasma volume and red cell volume separately. First the blood volume increases in pregnancy from 4000ml to a maximum of 5500ml by the 32nd week and decreases 200ml to 300ml thereafter, to fill the additional intra-vascular space caused by development of the placenta and the blood vessels. Furthermore, the plasma volume increases from the 10th week of pregnancy reaching a maximum of 3800 ml by the 32nd to 34th week. The total increase is about 1200 to 1500ml, which is 50% about the non-pregnant plasma volume. There it remains to term. Finally the red cell volume increases in a linear pattern to term from 1400ml in the non-pregnant to 1800ml in

the last three months of pregnancy. The increase peaks at 30%. In spite of this, the total increase in the red cell volume is proportionately less than the total increase in plasma volume. In this way the concentration of the red cells in the blood falls, with a reduction in the haemoglobin concentration. This has been called the physiological anaemia of pregnancy, but it is a misleading term for the pregnant woman has a larger total haemoglobin than when non-pregnant.

2.1.2 Changes in Circulation

Due to the high circulating levels of oestrogen, the stroke volume of the heart rises, and the heart rate also increases by about 15%. For this reason, the cardiac output increases by 30% to 50% in pregnancy, a rise from 5 litters per minute at the 10th week of pregnancy to 6.5 litters at about the 25th week for the purpose to deal with the increased blood volume and additional requirements for oxygen. The raised level is then maintained to term.

The increased cardiac output, owing to the effect of oestrogen and progesterone, is balanced by a reduction in the peripheral resistance of the blood vessels and consequently the blood pressure is altered only minimally.

The posture of the pregnant woman affects arterial pressure. Typically, blood pressure in the brachial artery is highest when sitting, lowest when lying in the lateral recumbent position, and significantly decreases when supine, sometimes referred to as the supine hypotensive syndrome. Usually, arterial blood pressure

decreases to a nadir during the second trimester or early third trimester and rises thereafter.

Otherwise, in the supine position, the large pregnant uterus may compress the aorta sufficiently to lower arterial blood pressure below the level of compression (Bieniarz J and associates, 1968). This demonstrated that the usual measurement of blood pressures in the brachial artery does not always provide a reliable estimate of the pressure in the uterine or other arteries that lie distal to aortic compression. When the pregnant woman is supine, uterine arterial pressure is significantly lower than that in the brachial artery.

2.1.3 The Distribution of Blood Flow in Uterus

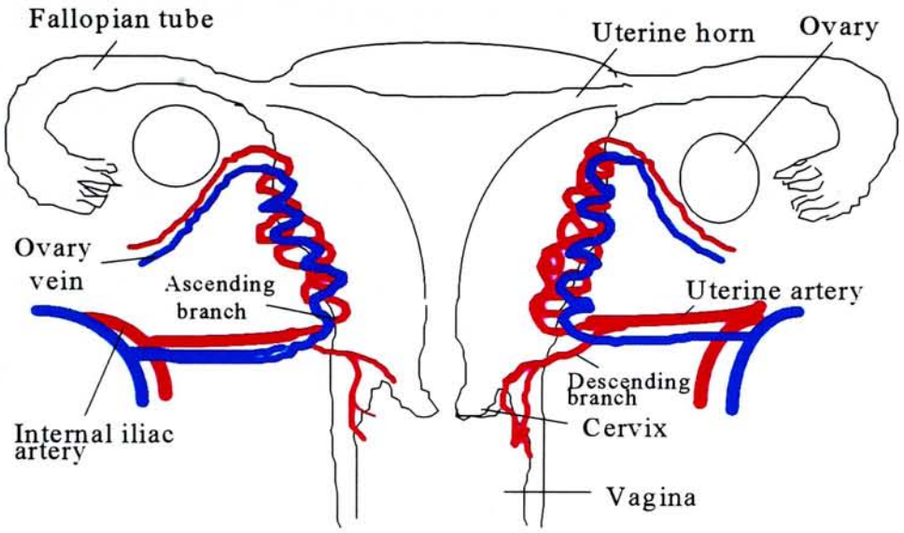
During pregnancy the uterus receives the greatest proportion of the increased blood flow. Recent evidence suggests that the flow increases from 75ml per minute at the 10th week of pregnancy to about 500ml in the 35th to 50th week. This increased uterine blood flow is believed to be essential for normal fetal growth and nutrition and for the avoidance of maternal hypertensive complications. At the moment of uterine systole, blood is forced under pressure into the choriodecidual space from the endometrial arteries, and spurts through the intervillous lake to reach the chorionic plate. The stream loses velocity, surrounds and cascades over frond-like villi, allowing an exchange of nutrients and waste

products to take place before it drains away through the endometrial veins in uterine diastole, to be replaced by a further spurt with the next systole.

2.2 Blood Supply to Uterus

The vascular supply of the uterus is derived basically from the uterine and ovarian arteries. The uterine artery is a main branch of the internal iliac artery, which enters the base of the broad ligament, and makes its way medially to the side of the uterus. In so doing, it crosses anterior to the side of the ureter at the point 2 cm lateral to the cervix. Immediately adjacent to the supra-vaginal portion of the cervix, the uterine artery is divided into two main branches. The smaller cervico-vaginal artery supplies blood to the lower portion of the cervix and the upper portion of the vagina. The main branch turns upward and extends thereafter as a highly convoluted vessel that traverses along the margin of the uterus; a branch of considerable size extends to the upper portion of the cervix and numerous other branches penetrate the body of the uterus. Just before the main branch of the uterine artery reaches the oviduct, it divides into three terminal branches: fundal, tubal and ovarian. The ovarian branch of the uterine artery anastomoses with the terminal branch of the ovarian artery; the tubal branch makes its way through the mesosalpinx and supplies part of the oviduct; and the fundal branch is distributed to the uppermost portion the uterus (Figure 2-1).

Figure 2-1 Vascular Supply of the Uterus



Branches of the uterine artery, the arcuate arteries, extend inward for a third of the thickness of the myometrium and encircle the uterus giving supply to the anterior and posterior walls. The radial arteries arise from the arcuate arteries and at right angles toward the uterine cavity. As these vessels enter the endometrium, they become the spiral arteries that undergo cyclic changes during the menstrual cycle. Approximately 100 spiral arteries connect the maternal circulation to the intervillous space during pregnancy. These vessels result in a tenfold increase in

the blood flow, which is required to catch up with the metabolic requirements of the fetus and placenta.

The ovarian artery, a direct branch of the aorta, enters the broad ligament through the infundibulo-pelvic ligament. At the ovarian hilum, it is divided into a number of smaller branches that enter the ovary. The main stem of the ovarian artery traverses the entire length of the broad ligament very near the mesosalpinx and makes its way to the upper portion of the lateral margin of the uterus, where it anastomoses with the ovarian branch of the uterine artery.

2.3 Pelvic Anatomy in Early Pregnancy via Transvaginal Sonography

Transvaginal sonography provides greater resolution of the pelvic organs than the conventional transabdominal sonography in early pregnancy. In this section, the normal anatomy of the uterus, ovary, and other adnexal and pelvic structures will be described as they would appear with transvaginal sonography..

2.3.1 Uterus

Examination of the uterus begins with its presentation in long axis. One can easily find the endometrium, which is typically, echogenic to be the landmark for evaluation.

When the endometrium is identified in long axis, the sagittal and transverse plane can be obtained. The uterine size (length, width and depth) can be measured about from $7\times4\times3$ cm^3 to $8\times5\times4$ cm^3 in non-pregnant state.

The volume of endometrium may be measured its long axis by the anterior-posterior (AP) width and transverse dimension. The thickness of the endometrium will change flowing the menstrual cycle. It is 4 to 8 mm and 8 to 12 mm as well as showing the hypoechoic inner layer in the proliferative phase and periovulatory separately. During the secretary phase, the endometrium is from 8 to 14 mm and is significantly echogenic. When the women come to postmenopausal stage, their uterus decreases in size and measure only 4 to 6 mm in long axis.

As the cervix becomes proximal to the probe under transvaginal examination, the image of cervix is not as clearly depicted as the rest of the uterus. In this condition one can withdraw the probe into the vagina and the image of the cervix can be obtained.

In early pregnancy, the uterus increases in size and the gestational sac, which appears as a 'double ring' in early first trimester, may be seen at the sagittal and transverse plane. The sac presents as a thick echogenic ring surrounding a sonolucent center, which is full of amnion fluid. The bilaminar embryonic disc and yolk sac may be seen. However the yolk sac can only be seen from the 5 to 12 or 14 week. Otherwise the embryonic cardiac activity can be seen from approximately 5.5 weeks from last menstrual period.

2.3.2 The Adnexa

The ovaries are beside the uterus and located along the pelvic sidewall. However in transvaginal sonography ovaries are typically situated anterior to the internal iliac vessels. The size of an ovary is approximately $3\times2\times2$ cm^3 in long axis, AP and transverse dimensions separately. Nevertheless it is altered with the patient's age and phase of follicular development. An ovary can become twice as large in volume while it contains a mature follicle.

The normal fallopian tube cannot be routinely visualised by transvaginal sonography due to its small size and serpiginous way. Occasionally one can identify the tube as an echogenic structure expanding from the uterine cornu toward the ovary. Its diameter is only 6 to 10 mm in a coronal plane.

2.3.3 Other Pelvic Structures

Directing the beam posteriorly may identify the pouch of Douglas. A small amount of fluid can be seen in the cul-de-sac in normal physiologic circumstances. The presence of significant amounts of free fluid suggests a haemorrhage or purulent condition. The appearances of the round ligaments are similar to a non-distended tube. The bowel appears as periodic intraluminal projections and with intraluminal fluid.

Chapter 3

Prostaglandin and Analogues

3. **Prostaglandins and Analogues**

Natural prostaglandins (PGs) are intimately involved in reproductive functions such as implantation and initiation of labour. PGE_2 and $PGF_{2\alpha}$ are the naturally occurring PGs.

3.1 Natural Prostaglandins

PGs are a series of enzymatic metabolites or peroxidating products of polyunsaturated (essential) fatty acid, especially contain C-20 carbon polyunsaturated fatty acid which has a special term "eicosanoids." The major natural source of eicosanoids is arachidonic acid. PGs were first identified by von Euler in 1935 to characterise the blood pressure lowering and smooth muscle tone modulating acidic lipids from human seminal fluid in prostate gland. They have been found throughout the body including the central nervous system, adrenals, liver, kidney and gut, where they are both humoural and neurotransmitter functions.

3.2 The Source of PGs in Reproductive Organs of Women

In the non-pregnant state, the endometrium is the main source of PGs whereas in the gravid uterus, the amnion, decidua and placenta all have a high synthetic capacity. Otherwise, PGs can be synthesised by platelets and many

white blood cells including macrophages, neutrophils, mast cells and some T cells, skin and stomach and there is growing awareness of its role in lymphoid cells. The major natural prostaglandin, PGE_1 is present in significant amounts in human seminal fluid.

PGE_1 has numerous biological activities such as modification of smooth muscle tone, adrenergic transmitter release, glandular secretion and platelet function as well as the inhibitory action on polymorphonuclear cells and immune response.

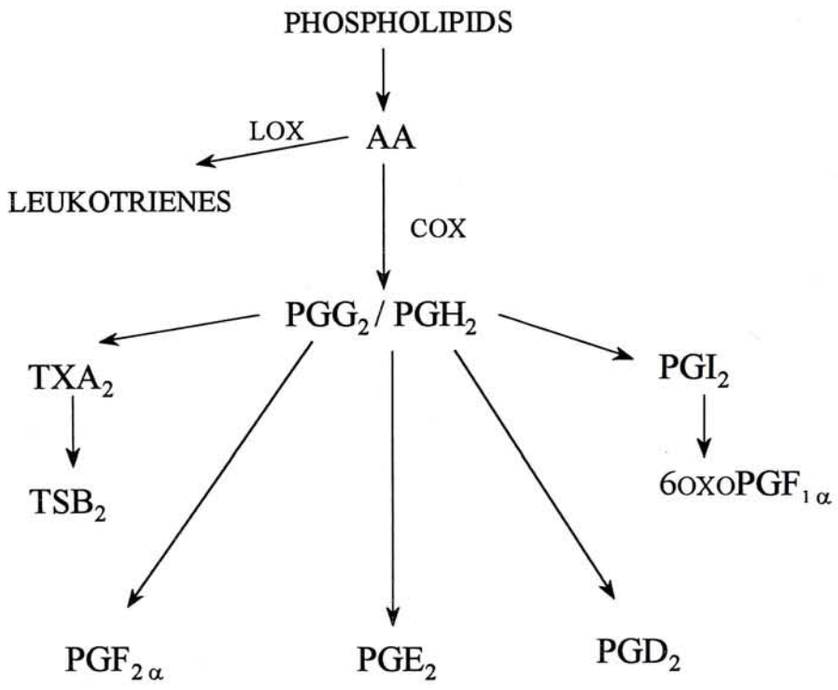
3.3 PGs Synthesis and Metabolism

PGs are synthesised on demand from precursor arachidonic acid (AA) by the action of phospholipases. Then AA is metabolised through the cyclooxygenase pathway to produce endoperoxides, PGG_2 and PGH_2, or by lipoxygenase toward leukotriene synthesis. The cyclic endoperoxides are unstable so are rapidly converted to primary PGs (PGD_2, PGE_2 and $PGF_{2\alpha}$) or via thromboxane or prostacyclin synthetase to thromboxane A_2 and prostacylin (PGI_2) respectively. The latter intermediates have short biological half-lives of 40 seconds and 3 minutes, and are converted into their stable products TXB_2 and 6-oxo $PGF_{1\alpha}$ (Figure 3-1).

There are three PGE-type prostaglandins: PGE_1, PGE_2 and PGE_3. They are synthesised from three unsaturated fatty acids, 8,11,14-eicosatrienoic acid,

5,8,11,14-eicosateraenoic acid (arachidonic acid) and 5,8,11,14,17-eicosapentaenoic acid respectively (Gréek K et al., 1981).

Figure 3-1 Metabolic Pathway of Natural Prostaglandins



The arachidonic acid cascade, illustrating the major uterine prostaglandin biosynthetic pathways. Lox = lipoxygenase, Cox = cyclo-oxygenase. AA = arachidonic acid, TX = thromboxane, PGI_2 = prostacylin.

3.4 PGE_1 Analogue: Misoprostol

PGE_1 analogues have been produced with similar structure to PGE_1. They have greater metabolic stability and hence greater activity when compared to the

natural compounds. There are 3 common PGE_1 analogues, gemeprost (other names: ONO-802, Cervagem), misoprostol (Cytotec) and sulprostone (Nalador).

3.4.1 Misoprostol

Misoprostol, DL-Methyl-11∝-16-dihydroxy-16-methyl-9-oxoprost-13E-en-1-oate,.was originally developed as a prophylactic against peptic ulceration in patients taking long term non steroidal anti-inflammatory drugs. Its chemical formula is $C_{22}H_{36}O_5$. It is a synthetic prostaglandin E_1 methyl ester analogue. Misoprostol in the Cytotec tablet form also contains hydroxypropyl methylcellulose 2910, microcrystalline cellulose, sodium starch glycolate and hydrogenated castor oil.

3.4.1.1 Pharmacology

Misoprostol is rapidly de-esterified to misoprostoic acid and intact misoprostol cannot be detected in plasma or urine. Misoprostoic acid may be detected in urine and plasma by radioimmunoassay (RIA). In man, misoprostol is rapidly absorbed, extensively metabolised and excreted. Approximately 80% of an oral dose is absorbed within 1.5 hours following administration. Peak levels of misoprostoic acid, the chief metabolite, occur within 12 to 30 minutes and

disappear with an elimination half life of 21-35 minutes (Foote EF et al., 1995). Excretion is prolonged in renal failure.

Misoprostol has major antisecretory effect mediated by the direct effect on the parietal cells of the stomach and mucosal cytoprotective properties on the stomach and duodenum. Divided daily oral doses of 1600 μgms have been reasonably tolerated apart from gastrointestinal discomfort. It has also been used vaginally in doses of up to 1,600 μgms in TOP without unacceptable side effects (Bugalho A et al., 1995).

3.4.1.2 Adverse Side Effects

The most common side effects are gastrointestinal; diarrhoea, cramp like abdominal pain and flatulence are dose dependent and occur in 10% of patients given the usual dose of 800 μgms per day (Walley TJ, 1993). Nausea and headache have also been reported. There are no known potentially hazardous drug interactions.

3.4.1.3 Toxicology

Dogs given massive overdoses (9 $mg.kg^{-1}$) develop tremors, mydriasis and diarrhoea. There is no known mutagenic potential. Large doses can lead to gastric hyperplasia in animals but this reverts to normal once misoprostol is

stopped. There is one report of a woman at a gestation of 31 weeks ingested a large amount of misoprostol and trifluoperazine (Stelazine). Manifestations of toxicity included hypertonic uterine contraction with fetal death, hyperthermia, rhabdomyolysis, hypoxaemia, respiratory alkalosis, and metabolic acidosis (Bond & Van Zee, 1994).

3.4.1.4 Misoprostol in Obstetrics & Gynaecology

In Obstetrics & Gynaecology, up to recently, it has been mainly used in therapeutic TOP in combination with an antiprogestogenic agent, mifepristone. A summary of the current uses of misoprostol and the other major PG analogue, gemeprost is shown below.

3.4.1.4.1 To Induce Abortion in First and Second Trimesters

The first application in O & G of PGE_1 analogues was to induce abortion and to apply its cervix-dilating action in second trimester (Sakmoto S et al., 1982). In this study the investigators used gemeprost by way of a vaginal suppository. Thereafter, for TOP, some investigators have used oral mifepristone (RU486) in combination with vaginal gemeprost in first trimester (Rodger MW et al., 1987; UK Multicenter trial, 1990) and others have used vaginal misoprostol only in the second trimester (Bugalho A et al., 1993).

Misoprostol has been used in TOP alone and combination with methotrexate in first trimester (Creinin MD, Vittinghoff E, 1994). Sixty three women were recruited for this study and were treated with either methotrexate 50mg per square meter of body surface area plus misoprostol 800μg or the same dose of misoprostol given alone. The misoprostol dose was repeated 24 hours later in case of abortion had not occurred. It was considered successful if the pregnancy ended without requiring a surgical procedure. They found complete abortion occurred in 14 (47%) of 30 patients in misoprostol alone and 28(90%) of 31 patients treated with methotextrate and misoprostol. They concluded methotrexate and vaginal misoprostol were more effective than misoprostol alone.

Misoprostol also has been used for abortion with mifepristone (RU 486) orally or vaginally in first trimester (el-Refaey H et al.,1995). Two hundred and seventy women were given mifepristone 600mg. If expulsion of the conceptus did not occur, a dose of misoprostol 800μg was given orally or vaginally. Expulsion of the conceptus without the need for a surgical procedure occurred in 95% of the women who received misoprostol vaginally and in 87% of women who received orally ($p<0.05$). Ninety three percent of the women receiving misoprostol vaginally had abortions within four hours, as compared with only 78% of the women receiving the drug orally ($p<0.001$). Vaginal administration of misoprostol was more effective and better tolerated than oral administration for the induction of first-trimester abortion after the administration of mifepristone. Moreover,

researchers using misoprostol in combination with mifepristone in first trimester have reported complete abortion rates in excess of 90% in the first trimester (Jing XP et al.,1995).

Misoprostol, given alone, has been reported in TOP in second trimester (Jain JK, Mishell DR Jr, 1994). Fifty-five women were include in the study. The efficacy and safety of 200μg misoprostol intravaginally every 12 hours and 20mg dinoprostone (PGE_2) intravaginally every 3 hours has been compared. The rate of successful abortion within 24 hours was 81% (22 of 27 women), compared with 89% (25 of 28 women) with misoprostol. The mean interval from treatment to abortion was 10.6 hours with dinoprostone and 12.0 hours with misoprostol. The rate of complete abortion was 32% for dinoprostone and 43% for misoprostol. The side effects such as pyrexia, uterine pain, vomiting and diarrhoea were more frequent in the women receiving dinoprostone than misoprostol. The authors concluded that misoprostol was at least as effective as PGE_2 for TOP in second trimester but with fewer side effects.

Misoprostol combined with mifepristone for TOP in second trimester has also conducted by el-Refaey H et al. (el-Refaey H, Templeton A, 1995). Seventy women were pre-treated with mifepristone. Abortion was achieved in 97% of cases. The mean induction abortion time was 6.4 hours. The authors reported that there were no significant differences between vaginal or a combination of vaginal and oral administration. They recommended that following pre-treatment with

mifepristone, misoprostol was the prostaglandin of choice to induce abortion in the second trimester.

The clinical efficacy of misoprostol and gemeprost for second trimester TOP has been examined (el-Refaey H et al., 1993). Sixty women were allocated into two prostaglandin regimens following pre-treatment with mifepristone 600 mg. The first was given misoprostol 400μg orally followed by gemeprost vaginal pessary 1 mg. The second was only gemeprost vaginal pessary 1 mg. There was no significant differences in the outcomes between the two groups.

3.4.1.4.2 Cervix Priming prior to Surgical Evacuation of Uterus

Cervical laceration is a known complication of surgical evacuation of the uterus in TOP. Priming with misoprostol to soften and dilate the cervix can reduce mechanical force required and hence reduce the chance of trauma. Since Sakmoto S et al. (1982) demonstrated that PGE_1 analogue, gemeprost, could be used to soften the cervix, studies have been conducted into the clinical utility of gemeprost and misoprostol for cervical dilation to facilitate first trimester TOP (Welch C, Elder MG, 1982; Bugalho A et al., 1994, el-Refaey H et al., 1994).

Edwards D et al. have studied 595 patients who were given misoprostol orally 30 to 60 minutes before surgical TOP. They reported that patients given a total dose of 600μg misoprostol were more likely (22%) to have cervices which

were easy to dilate than those receiving 400μg of misoprostol (Edwards at al., 1994).

3.4.1.4.3 Medical Management of Miscarriage

The earlier diagnosis of miscarriage by sonography has become more common and more conservative methods of uterine evacuation have been used. The current standard management for spontaneous abortion is surgical evacuation. However, in recent years, there have been a number of studies that have shown that PG analogues can be effective in evacuating a proportion of uteruses where there are retained products of gestation (Chung T et al., 1994). In a study of 132 patients with retained products of gestation proven on TVS, gemeprost vaginal suppositories every 3 hours was able to empty the uterus in just under 50 % of cases. The same authors conducted another 2 studies using misoprostol (Chung TK et al, 1995, 1996) and found that misoprostol given orally was able to empty uteruses which has retained products of gestation by TVS in about 50-67 % of cases. Oral misoprostol has been used to treat missed abortion and brighted ovum (el-Refaey H et al, 1992). Some researchers have used sulprostone (PGE_2 analogue) and misoprostol to manage incomplete or inevitable abortion (Henshaw RC et al, 1993).

3.4.1.4.4 Induction of Labour with Dead Fetus

The first use of misoprostol for labour induction in stillbirth was reported by Mariani-Neto et al. in 1987. They studied 20 patients with gestation of 19-41 weeks who presented with in-utero fetal death. Four hundred μg of misoprostol was administered orally every 4 hours until delivery occurred. They reported that all dead fetuses were delivered successfully with a mean induction-to-delivery interval of 9 hours and 12 minutes.

Bugalho A et al. in Maputo used vaginal misoprostol suppositories as an alternative to IV oxytocin for induction of labour with late fetal death (Bugalho A et al., 1995). In this study, 156 women were enrolled and the induction-to-delivery interval in misoprostol group was shorter than in oxytocin group with Bishop's score <6, ≥6 or with intact membranes. Successful rate of induction reached 81% of misoprostol-treated women at a dose of 100 μg or less.

3.4.1.4.5 Induction of labour

Misoprostol has been used for labour induction in viable state (Margulies M et al., 1992; Sanchez-Ramos L et al., 1993). The first had two studies -- a dose-finding study and a comparative trial of misoprostol and oxytocin. The former study determined that misoprostol doses required averaged 162 μg and 188μg for patients with gestation age 28-36 weeks and more than 36 weeks respectively. The latter study was a randomised controlled trial comparing 50 μg misoprostol

given intravaginally with IV oxytocin in 64 patients whose labours have been induced. The authors concluded that misoprostol is effective in the induction of labour and there were few maternal side effects and no apparent adverse effects on the new-born.

In second study, the investigators compared misoprostol administered intravaginal with IV oxytocin in 129 patients and demonstrated that intravaginal administration of misoprostol safely and effectively induced labour - while minimising the expense associated with IV oxytocin infusion. Excessive uterine contractions occurred more frequently in patients in the misoprostol group but did not increase the risk of adverse intrapartum or perinatal outcomes. However, the sample size of this study was two small to be confident of detecting a difference in perinatal and intrapartum outcomes if one exists.

3.4.2 The Potential Dangers of PGE_1 analogues

Misoprostol has become more popular in O & G because of its low cost, convenient storage. However, its use in the induction of labour should be viewed with some caution at present

There have been some reports about the use of misoprostol in labour-induction causing excessive uterine contractions. However, apparently this did not increase the risk of adverse intrapartum or perinatal outcomes (Sanchez-Ramos L et al., 1993). In this study, continuous electronic fetal heart rate monitoring

(including an intrauterine pressure catheter and scalp electrode). Margulies M et al. who studied 56 patients found that no adverse effects on the fetus or baby were observed. However, they observed systole more frequently in misoprostol group compared to the oxytocin group, but no fetal distress was associated with this condition in either groups. However, in this study, there was no universal continuous fetal monitoring.

Misoprostol has been compared with intravenous (IV) oxytocin for the induction of labour. Sixty four subjects with a singleton pregnancy were recruited. Thirty-three patients were given 50μg misoprostol and 31 were given intravenous oxtocin. Success was defined as the woman going into labour. A 79% successful rate was found in the misoprostol group compared to 62% in the oxytocin group. One patient was delivered by caesarean section because of fetal distress in misoprostol group and 3 in the oxytocin group.

Misoprostol has been used for cervical priming in pre-labour rupture of membranes (ROM) at term (Ngai SW et al., 1996). Eighty patients were recruited and randomised to receive 200μg misoprostol or 50 mg vitamin B_6 orally. If the patient did not go into labour 12 hours after oral medication with either misoprostol or vitamin B_6, intravenous oxytocin infusion was started. The study found that the proportion of patients requiring oxytocin induction was lower (15%) in the misoprostol group than in the placebo group (51%) ($P < 0.001$). The perinatal outcomes were similar in the two groups. So the investigators concluded

misoprostol at a dose of 200μg is effective for cervical priming in patients with pre-labour ROM at term. These results were consistent with those of Marguiles et al. (1992).

Chapter 4

Doppler Sonography and Parameter Measurement

4. Doppler Sonography and Parameter Measurements

The principles of ultra-sonography and Doppler apparatus will be discussed below. This chapter will focus on how many and what kinds of commonly used methods of blood flow measurement, as well as how to measure the blood velocity of the uterus. Both continuous waves Doppler (CWD) and pulsed waves Doppler (PWD) have been used in the investigation of the UA. As the waveforms of UA are influenced by the site where the waveforms are obtained, as well as other factors such as the hormone, the resistance and diameter of the vessel etc., this chapter will also try to explore what the effects of those factors and the components of the waveforms are, as well as to demonstrate the waveform changes of uterine arteries in the whole pregnant state.

4.1 The Principles of Ultrasound and Doppler Sonography

4.1.1 The Basic Principles of Ultrasound

Ultrasound is a mechanical pressure wave. Its frequency is inaudible to the human ear and is usually beyond 20 to 20,000 cycles per second (Hz). The frequencies used in medical diagnosis are generally between 1 and 15 Megahertz (MHz). Diagnostic ultrasound used in O & G is usually between 3 to 7.5 MHz. Ultrasound has the same characteristics as sound, which is frequency, wavelength, amplitude, intensity, and propagation speed. When it passes through the different

boundaries in different angles, it has the phenomenon such as reflection, refraction absorption and scattering.

The generation of ultrasound waves is based on the behaviour of the piezoelectric effect of certain materials, such as resins, crystals, or ceramics. An electronic voltage is generated while a crystal is compressed. It is the so called 'piezoelectric effect.' Reversibly the application of a voltage through a crystal may induce compression or expansion inside. That is why electrical stimulation on piezoelectric materials can induce mechanical deformation, which can produce waves at ultrasonic frequencies. This phenomenon also operates in reverse: the echoed mechanical waves generate electrical signals, which can be recorded and analysed.

Most crystals do not possess the property of piezoelectricity and the most important natural crystal possessing this property is quartz. It has been used in ultrasonic generators for many years but now it has been replaced in medical devices almost completely by synthetic ceramic crystals, barium titanate and lead zirconate titanate (PZT), for these have better mechanical properties and are easier to fabricate compared to quartz.

When ultrasound pulses are transmitted into the tissue interface, a returning pulse or echo is generated to the point with different acoustic impedance. The average speed of sound passed through the soft tissue is uniformly calculated at 1,540 meters per second. Then we can calculate the distance to the source of the

returning echoes. The intensity of the echo determines the brightness of the dot at that point on the screen. To create an updated imaging, which is the 'real-time' imaging, the frame rate must be greater than the flicker-fusion rate of the eye, which is about 15 cycles per second or greater. This is considered adequate.

According to the display of returning echoes, the techniques most used in clinic practice are: A-Mode (Amplitude mode), B-Mode (Brightness mode), M-Mode (Motion mode) and Doppler type.

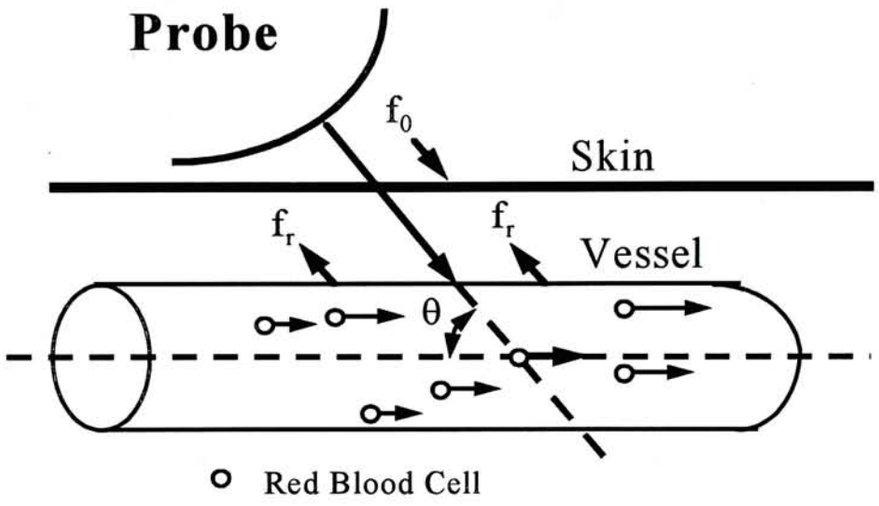
4.1.2 Principles of Doppler Sonography

The Doppler principle is that when energy is reflected from a moving boundary, the frequency of the reflected energy varies in relation to velocity of the moving boundary. That is the Doppler effect described by Austrian physicist - Christian Johann Doppler in 1842 (Doppler JC, 1842) and verified in 1845 by Dutch mathematician - C.H.D. Buys Ballot in a famous railroad engine experiment (Fleischer AC et al., 1994).

In clinical use, the transmission and receiving sources are stationary and the change in path length results from movement of the target either toward or away from these transducers. In studies of blood flow, the moving column of blood within the studied vessels is the target. The red blood cells acted as scatters reflect the ultrasound beam. The frequency of sound reflected off moving blood cells are altered to the sound emitted from the transducer on the velocity of the blood.

From the equation (showed inFigure 4-1), the change of frequency is known as the Doppler frequency shifts and is dependent on the moving object and the angle between the insonation beam and the direction of motion. If the beam's angle of insonation is known and the frequency shift can be determined, from the above equation we can convert to velocity of blood flow.

Figure 4-1 Doppler equation, obtained from the Doppler frequency shift in vessels, relations to angle of interrogation.



$$\Delta f = f_r - f_0 = \frac{2 f_0 v}{c} \cos\theta$$

$$\Delta F = \frac{2F_0\, V\, (\cos\theta)}{C} \quad \text{or} \quad V = \frac{Fr\,(C)}{2F_0\,(\cos\theta)}$$

where

F_0 = the frequency of the emitting source in cycles/s

V = the velocity of blood flow

cos θ = the cosine of the angle of insonation

C = the velocity of sound in tissue 1540 m/s

ΔF = the difference in frequency between the emitted and returning sound

Fr =the returned frequency

4.2 Doppler Mode

There are three types of Doppler ultrasound used in modern diagnostic equipment. They are continuous wave Doppler, pulsed wave Doppler, and two-dimensional colour flow mapping.

4.2.1 Continuous Wave Doppler Imaging

In this system a single transducer either transmits or receives the ultrasound signals. There are two piezoelectric elements within the transducer: one continuously transmits while the other continuously receives reflected echoes. In such way the transmitted beam and the area of reception of echoes overlap. A continuous wave system will receive all Doppler-shifted waves from the reception zone but is unable to distinguish the site of origin of the echo signals. It is widely used in fetal heart rate monitoring, as well as in the Doppler assessment of uterine-umbilical blood flow.

4.2.2 Pulsed Wave Doppler Systems

Unlike continuous wave Doppler system, in this system ultrasound beam is transmitted in a pulsed fashion, and when not transmitting, the same crystal serves as a receiver for returning echoes. Current pulsed Doppler machines are of the

duplex type, which allows the same transducer to ultrasonically guide placement of the sample volume over the desired vessels and assess Doppler shift signals indicating flow velocity.

4.2.3 Colour Doppler Sonography (CDS)

Colour flow sonography involves the addition of colour to the ultrasound image to indicate direction of blood flow. Flow toward the transducer is represented by the colour red while flow away from the transducer is presented the colour blue. This flow information is then superimposed on the two-dimensional real-time images to form the complete colour Doppler sonogram. So it offers a new method to study circulation.

The calculation of the blood velocity is shown in Figure 4-1. As can be seen, it is independent of the angle of insonnation, which allows for 1 source of possible error to be eliminated.

4.3 The Instrument of Doppler Sonography

Sonography originated in the 1940s, but application in O & G began in 1958. Later, Barber FE and others in 1974 successfully combined real-time sonography and Doppler to direct the Doppler beam more accurately.

A sonographic system basically consists the following four sections:

1. A chief equipment that is an electronic signal processing unit with controls for power output and has the function of receiving and magnifying the electronic signal.
2. A transducer (also called probe) with the piezoelectric crystals in it so as to change the electrical signal to ultrasound wave and verse visa. It comes in a variety of shapes and sizes. Some of the more common types are cylindrical, flat, perivascular, aspiration, and multi element transducer arrays.
3. A gray scale unit to adjust the contrast and brightness of the image.
4. A screen to record the images permanently.

A Doppler ultrasound unit usually connects with an ultrasound scanning system and creates both high resolution images of internal blood vessels and the simultaneous values of blood flow velocity within them. Table 4-1will illustrate the components of a Doppler ultrasound unit:

Table 4-1 Components of a Ultrasound Machine

Transducer	Central Unit	Output
A. Transmitting crystal(s) (Constant Frequency)	Frequency changes detected	A. Visual 1. Oscilloscope screen 2. Strip Chart
B. Receiving Crystal(s)		B. Audible Sounds

It is clear that based on the ultrasound system, a Doppler ultrasound unit may add several output formats: audible sounds, waves on an oscilloscope screen, or a tracing on a continuously moving paper chart.

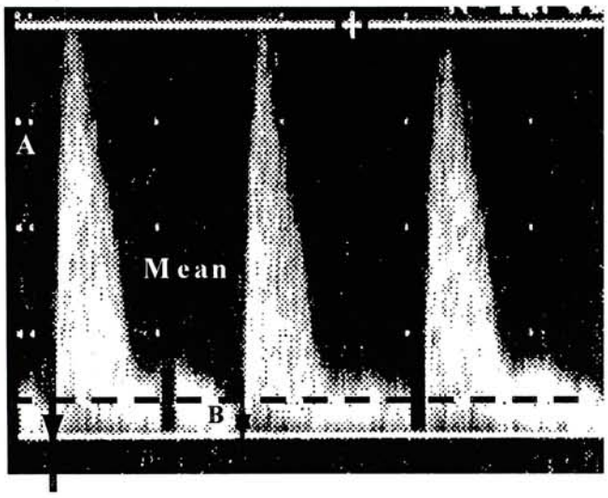
4.4 Resistance Indices -- S/D, PI and RI

A waveform is the Doppler signal displayed on the monitor produced by and representing the Doppler shifts created by circulating red cells during a cardiac cycle. If Doppler signals produce a shift toward the transducer, an upward displacement of the baseline will display on the monitor while those signals producing a shift away from the transducer will display as a downward shift from baseline.

The most commonly used indices are systolic flow velocity /diastolic flow velocity ratio (S/D ratio), resistance index, and pulsatility index (PI) as shown below in Figure 4-2.

These three indices are independent of the incident angle as cos θ in both the numerator and denominator cancel out and do not need to measure the diameter of the vessel. According to this benefit, clinicians usually like to use these indices to detect the resistance of vessels, especially in Obstetrics because the vessels studied are often too small to measure accurately and too tortuous to

Figure 4-2 Quantitative Methods of Waveform Analysis



$\frac{A-B}{Mean}$ = **Pulsatility Index**
(Gosling and King 1975)

$\frac{A}{B}$ **Ratio (or S/D Ratio)**
(Stuart et al 1980)

$\frac{A-B}{A}$ = **Resistance Index**
(Pourcelot 1974)

A - Peak systolic flow
B - End diastolic flow
Mean - Mean Velocity

determine the angle of insonation (for example, umbilical artery or uterine artery). However, these indices can be affected by fetal breathing (Indik JK, Reed KL, 1990), fetal heart rate abnormalities (Reed KL et al., 1987), and fetal movements(van Eyck J et al., 1985). Therefore the A/B ratio, PI and RI should be measured during the periods of fetal apnoea.

Some work has been done to assess other features of the waveform such as acceleration time, deceleration time, volume flow, etc. However it shows no advantage over the previously mentioned three indices.

4.5 Flow Measurement of Uterine artery

4.5.1 Sampling Sites and Waveforms

There are four different parauterine vessels which are sample sites for measuring the flow velocity waveforms. They are external iliac artery, uterine artery near its origin, arcuate branches near the placenta bed (Schulman H et al., 1986) and the subplacental vessels (Trudinger BJ et al.,1985). The subplacental vessels and arcuate vessels have the highest diastolic frequency and have the lowest ratios. The external iliac vessels have no end-diastolic velocity but a prominent notch because of the high resistance. Otherwise, the main uterine arteries have a higher systolic component. Sometimes a significant notch is seen in the first trimester. UA waveforms obtained from the site as it crosses the external iliac artery are the same as the site near its origin from the internal iliac artery (Oosterhof H, Aarnoudse JG, 1992). One can easily locate the main uterine artery using the colour Doppler imaging while it crosses the external iliac artery. Arcuate, radial and spiral arteries have high sampling bias, and are extremely difficult to reproduce and do not reflect the whole utero-placental circulation (Bewley S et al, 1989). Investigators usually use the main uterine arteries to reflect the total resistance to blood flow in the utero-placental circulation.

4.5.2 Waveform Components

The total flow waveform is divided into two parts: a pulsatile component and a steady component. The pulsatile flow waveform is subdivided into an outgoing wave and a reflected wave. The former generates through the contraction of heart and propagates towards the peripheral vessels. The latter reflects the wave that bounces back to the heart from the utero-placental bed, so its waveform is inverted to the outgoing waveform. Combination of the outgoing and reflected waves produces the total pulsatile component of the flow waveform. Attaching the steady flow to the pulsatile component will create the total flow waveform (Adamson SL et al., 1989). If we know the cross-sectional area of the blood vessel, then the velocity can be calculated from the total flow waveform.

4.5.3 Identification of the Main Uterine Arteries

The main uterine artery is the segment of the artery arising from the internal iliac artery to the lateral aspect of the cervix. There, it divides into the uterine and vaginal branches. Both colour Doppler and pulsed Doppler can be used to identify the uterine artery (Kurjak A et al., 1991). The details of identification of the UA will be discussed in section 6.

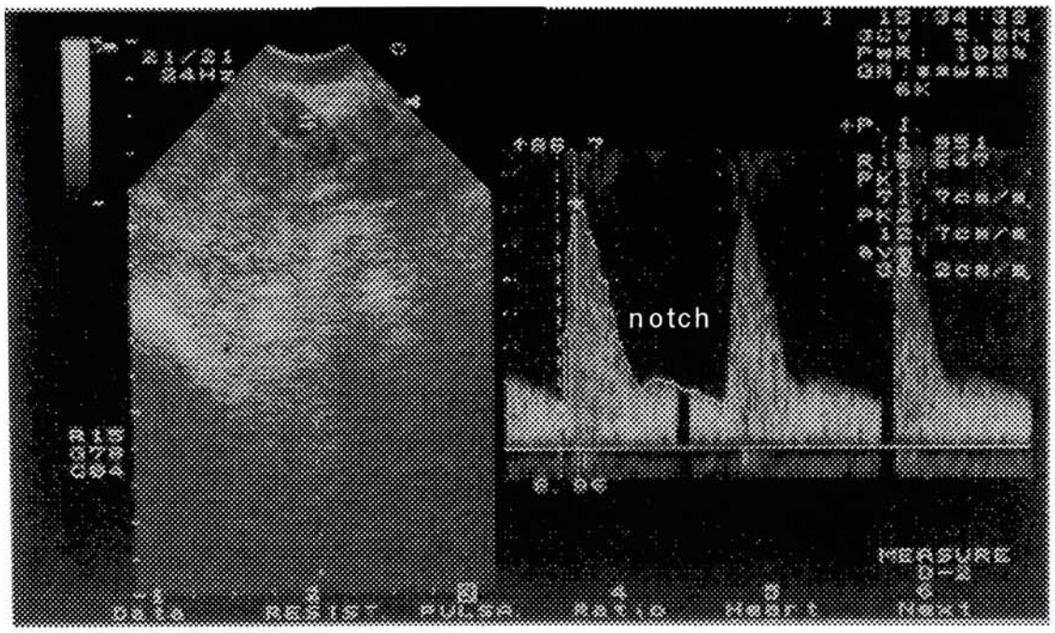
4.5.4 UA Waveform Changes in Normal Pregnancy

In first trimester, the compliance of UA rises initially and then falls. Consequently, a prominent diastolic component can be detected as early as the fifth week of gestation. Following this, the resistance index gradually decreases from the sixth to the twelfth weeks (Mercé LT et al., 1989). So the waveforms obtained from UA, occurring in the way of elevated S/D ratios and reduced end-diastolic velocities, presents with a dicrotic notch in the systolic deceleration slope (Schulman H et al., 1986) (Figure 4-3). The dicrotic notch was thought to be a reflection of a reflected wave of high amplitude returning from a utero-placental bed while the vascular resistance is elevated (Mo LY et al., 1988).

Coming to the second trimester, the vascular resistance decreases as gestation progresses with a progressive increase in the cross-sectional area of the uterine artery, as well as the morphologic changes of the spiral arteries in the placental bed.

After 24 to 26 weeks of gestation, the early diastolic notch should completely disappear, so as the difference of S/D ratios between placental sites to non-placental sites (Schulman H et al., 1986). Any abnormality such as elevated resistance index and the diastolic notch appearing after 24 to 26 weeks may indicate preeclampsia or small-for-gestational-age fetuses (Trudinger BJ et al., 1985).

Figure 4-3 The Doppler waveform from left uterine artery shows the notch in the systolic deceleration slope in early pregnancy.



In the first 24 hours postpartum, the S/D ratio increases and the blood velocity remains high. By the second day postpartum, both S/D ratio and PI increase and the diastolic notch reappears until the sixth puerperal week. After that, the resistance indices start to rise again until the third puerperal month (Thoresen M, Jarlis W, 1988).

4.5.5 Factors Affecting the UA Waveforms

The placental site can affect the UA waveforms. For example, compared with the uterine artery at the point where it crosses the external iliac artery, a significantly lower pulsatility index (PI) value was found in the arcuate arteries near the placenta bed (Oosterhof H, Aarnoudse JG, 1992).

Otherwise, some authors have developed a computer modelling to study the factors that determine velocity waveform shape. They found that the utero-placental vascular resistance, uterine arterial diameter and the blood pressure all have the effect on the uterine arterial velocity waveform (Mo et al,1988; Adamson SL,1989). If utero-placental resistance increase, the systolic/diastolic velocity (S/D) ratio and pulsatility index of the waveform will increase. However, a dicrotic notch will appear. If the radius of the uterine artery is reduced, the S/D ratio and PI can increase. In this case, however, a dicrotic notch is not produced. On the other hand, if the mean arterial pressure in the uterine artery increases, there is almost no change in S/D ratio or PI.

Moreover, the hormones, oestrogen and progesterone, also affect the uterine circulation. This may be due to the oestrogen receptors occurring in the wall of human uterine arteries (Perrot-Applanat M et al., 1988). Those patients with absent ovaries, their baseline estimation show narrow systolic Doppler flow waves with a pulsatility index of 5.2±0.4 (mean±SEM). The elevation of plasma oestradiol (E2) and progesterone can induce a profound decrease in the vascular

resistance and an uninterrupted flow signal during the diastolic interval (de Ziegler D et al., 1991).

4.5.6 Uterine Artery Resistance in Normal Pregnancy and Labour

Several authors have studied the changes of the uterine blood flow, usually using the resistance indices from the non-pregnant state to the early pregnancy and until term in normal situation. This chapter will review the above items separately.

4.5.6.1 Uterine Artery Resistance in Normal Pregnancy

Doppler ultrasound provides a non-invasive approach of measurement of blood flow velocity. Since the ratio of peak systolic to diastolic flow velocity was used as a measure of downstream resistance (Gosling RG, King DH, 1974), a method of recording flow velocity-time waveforms of the uterine artery using pulsed Doppler ultrasound has been reported (Campbell S et al., 1983).

There have been some investigations on the resistance indices of uterine artery in normal pregnancy. In first trimester, the resistance index shows a gradual weekly decrease, with significant differences before [(S-D)/S = 0.83±.09] Vs after the 9th week [(S-D)/S = 0.72±0.10] (Mercé LT et al., 1989). This study enrolled twenty-five early singleton pregnant women from 7 to 13 weeks from the last menstrual period and found that a highly resistant systemic vessel with an elevated

systolic peak and reduced end-diastolic flow. Otherwise, a notch is present in the systolic deceleration slope.

Trudinger BJ et al. in 1985 had studied twelve normal pregnancies from 20 weeks to delivery and concluded that there was a small decrease S/D ratio with gestational age indicative of a decreasing flow resistance (Trudinger BJ et al., 1985).

Changes in uterine blood flow during human pregnancy, which from non pregnant state to term, have been explored. Thaler et al. studied 24 patients and found that S/D ratio declined from a mean of 5.3 in the non-pregnant state to mean of 2.3 near term (Thaler I et al., 1990).

In conclusion, resistance to flow decreases in the utero-placental-umbilical circulation as gestational age increase in normal pregnancy mainly due to the forward diastolic flow increasing with gestation age. The changes in flow are reflected in the decrease of the Doppler indices: S/D ratio, RI, PI. The decreasing in these indices means the falls in the resistance of blood vessel in the utero-placental-umbilical circulation. The increasing in blood flow may have the advantage for the fetus.

4.5.6.2 Uterine Artery Resistance during normal labour

It is important to understand the normal changes of uterine artery resistance in labour. It may help us to be aware of the abnormal condition and what it will be potentially harmful to the fetus.

In labour, the frequency of uterine contractions rises and the intrauterine pressure increases. Fleischer A et al. have studied uterine and umbilical artery velocimetry during normal labour (Fleischer A et al., 1987). They have observed 12 patients throughout the three stages of labour and found that the uterine artery waveforms changed during contraction. Before labour, the changes in uterine artery velocity waveforms consist of the loss of diastolic notch and a progressive decrease in the S/D ratio (Schulman H et al., 1986). During the uterine contractions in labour, the spiral arteries are being constricted in proportion to the intensity of the contraction. The impact of these changes on the uterine artery waveforms is a progressive fall of the diastolic blood flow velocity. The degree of changes is related to the intensity of the uterine contraction. During the period of contraction, the end-diastolic velocity even reaches zero when the intrauterine pressure is over 35 mmHg. Where there is intrauterine pressure greater than 60 mm Hg, no diastolic notch was detected. The authors concluded that the end-diastolic component is primarily determined by changes in the arcuate and spiral arteries. However, they did not report the changes of the values of resistance indices, during three stage on the uterine arteries.

Maymon R et al. have studied the changes in uterine artery velocity waveforms during the third stage of labour (Maymon R et al., 1995). They observed three phases of the third stage of labour and found S/D ratio and PI of uterine artery were 2.14 ± 0.53 and 1.28 ± 0.37 respectively in latent phase, 2.53 ± 0.53 and 1.28 ± 0.37 respectively during a contraction and, 2.20 ± 0.34 and 0.91 ± 0.20 respectively in expulsion phase ($p<0.05$). They concluded that the uterine artery Doppler flow velocity waveforms reflected by a high resistance flow according to the increase of resistance due to the uterine contractions. Up to now, the candidate is not aware of any studies which has examined the changes of resistance indices of UAs during the first and second stages of labour.

4.5.7 Doppler Measure of Fetal Heart Rate

The variation of fetal heart rate can reflect fetal status in the uterus, especially during delivering. It has developed many methods for monitoring the fetus, such as fetal ECG from maternal wall or ultrasonography.

There is little information to describe the normal ranges of FHR in first trimester. The vagus nerve may play an important role in the progress of FHR. From 15th gestational week to term, FHR reduces with advancing gestational age in normal pregnancy (Stuart B et al., 1984; Robinson S, 1991). FHR at 18 weeks is about 148±5 bpm. There are no differences in fetal heart rate between the sexes

at 18 weeks gestation. However, by 36 weeks the boys had rates which were 4.4 beats lower than those of the girls (95% CI is 0.8-8.0, P=0.02) (Robinson S, 1991).

At term, the normal ranges of FHR is 120 to 160 beats per minute (bpm). Less than 120 bpm is defined as bradycardia and more than 160 is tachycardia. Fetal bradycardia may be related to hypoxia, while fetal tachycardia is possible due to fetal distress. Fetal breathing, drugs, fetal movement (rest or activity) may lead to FHR variation. To use Doppler measuring FHR, one can calculate the time interval between two cardiac cycles.

4.6 Sonography in Estimation of Gestational Age

The widespread dissemination of sonography has enabled routine visualisation of the pregnancy at the first antenatal visit. With the endovaginal sonography (TVS), we are able to precisely date the pregnancy; to directly diagnose ectopic pregnancy or at least to suspect it. So diagnosis can precede rupture, and allow management to be more conservative and less destructive; to definitively diagnose its failure before spontaneous passage, or to identify the completed abortion from incomplete and missed abortion. In such way, the medical or non-surgical treatment is possible (Mansur MM, 1992; Rulin MC et al., 1993; Haines CJ et al., 1994).

In the first trimester pregnancy, gestational sac and crown-rump length (CRL) can now established the gestational age. The most accurate prediction of

menstrual age would be obtained by measuring the gestation sac among 5-6.5 weeks. After 6.5 weeks, there is an alternative measurement, the CRL (Robinson HP et al., 1975; Drumm JE, 1977). Bi-parietal diameter (BPD) and femur length (FL) are the common used parameters in the second and third trimester measurements. However, in the late second and third trimesters, increasing error are introduced so that estimation of gestation becomes increasingly unreliable.

Chapter 5

Research Protocol

5. **Research Protocol**

This chapter describes the research protocol in detail.

5.1 The Ethics

This study described in this thesis was carried out in accordance of the code of ethics described in the Declaration of Helsinki and last amended in 1989 (World Medical Association Declaration, 1989). It states that it is the mission of the medical doctor to safeguard the health of the people. His or her knowledge and conscience are dedicated towards the fulfilment of this mission. The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

This aim of the study was to determine the effects of misoprostol on the resistance indices of the utero-placental circulation via an examination of the blood flow velocity of the uterine arteries (UAs). This research is worthwhile because it can yield useful information on the impact of the administration of a small dose of misoprostol on the utero-placental circulation. Misoprostol may have potential dangers to the fetus in late pregnancy where it is now being used to induce labour where there is a viable pregnancy.

Misoprostol has a low incidence of side effects and are mainly dose dependent and most are gastrointestinal in nature. The fact that administration of

this drug may be dangerous in these cases is accepted because these women had been admitted for TOP where the fetal welfare is not a point of consideration. The main concern in this case is the safety of the medication to the mother. Adverse effects such as diarrhoea were thought to be acceptable because misoprostol is of therapeutic value for the subjects involved in the study as it acts as a priming agent for the cervix prior to TOP. This therapeutic value is independent of the research being carried out.

This study was conducted with the subject being fully conscious at all times. She was also aware that a portion of the interventions was purely research in nature and that she is at liberty to withdraw from the study at any time. They were specifically counselled that should they refuse to participate in the study that this refusal will not compromise their clinical care.

This research was approved by the Ethics Committee of The Chinese University of Hong Kong. Before recruitment, all subjects were counselled about the research protocol and gave both verbal and written consent (appendix I or II).

5.2 Apparatus

A Doppler ultrasound system with a 5.0 MHz curvilinear transvaginal probe (Aloka UST-980P-5 , Aloka Co., Ltd) was used. The apparatus, Aloka Echo Camera SSD-2000 (Aloka Co., Ltd), was equipped with only non-coloured pulsed Doppler. The high-pass filter was set at 50 or 100 Hz . The apparatus used is shown in Figure 5-1.

Figure 5-1 Apparatus Used in Study

5.3 Drug and Dosage

Subjects who had no any contradictions were given misoprostol 200μg (DL-methyl-11a-16-dihydroxy-16-methyl -9- oxoprost- 13E - en-1-oate; Cytotec, Searle) by oral administration.

5.4 Research Protocol

5.4.1 Subjects

Subjects with a normal singleton intrauterine pregnancy of 7-15 completed gestational weeks were recruited for the study. All the subjects had been admitted for legal, surgical TOP. The inclusion criteria were the presence of normal singleton intrauterine pregnancy. Those subjects were excluded from the study when they had:

1. Asthma
2. Heart disease
3. Glaucoma
4. Known allergy to prostaglandins
5. History of epilepsy

All study subjects recruited were counselled and signed a specific consent form (Appendix I or II).

A before and after administration of misoprostol effect on the resistance indices was measured. The difference between these 2 measurements (delta) was used to measure the effect of misoprostol. The hypothesis was that the delta value would deviate significantly against the expected zero. The candidate acknowledges that this method has no proper control group and that these changes observed cannot be compared against a proper control group of women who had 2 TVS examinations without any active intervention or placebo in between.

5.4.2 Transvaginal Scan

Then the first ultrasound scan was performed. Before the scanning, the subjects were prepared lying in a supine position on the examination table with their knees bent. The following features were noted on each scan:

1. If the gestational sac is single
2. If the fetal pole is present
3. If the embryo or fetus is viable
4. What is the CRL or BPD of the fetus
5. If the adnexa of uterus is normal
6. If there is free fluid in POD

All subjects who had an abnormal pregnancy such as missed abortion, blighted ovum, mole pregnancy, ectopic pregnancy and multiple pregnancies were excluded from the study.

5.4.3 Parameters Measured

Following the assessment of the pregnancy, using the Doppler ultrasound apparatus, the study parameters were measured. Those were FHR, S/D ratios and PI of left or right main uterine arteries (LS/D, RS/D, LPI, RPI) (Figure 5-2to Figure 5-4).

The UA were examined at the level of the internal os as the artery approaches the uterus laterally (Figure 5-5). The internal os is visualised in the sagittal plane. The probe is then turned into the transverse position and then angled upwards towards the long axis of the uterus. The vascular bundles are then easily visualised and pulsations that can be seen in real time help identify the uterine arteries. The characteristic blood flow velocity waveforms were then obtained by placing the Doppler gate over the identified area. Initially, a number of examinations were done with the aid of colour Doppler facility. However, this machine became unavailable before the commencement of the study proper. Nevertheless, by using the method described above, it was relatively easy to visualise the uterine arteries and obtain the characteristic wave forms.

For Doppler measurement colour Doppler was not available but the anatomical landmarks were used. This was based on the identification of the UA waveform which a characteristic notch existed in the systolic deceleration slope as mentioned in 4.5.5 before 20 to 24 weeks gestation, as well as a high systolic

velocity. This typical appearance can help us to exclude the waveforms of arcuate arteries and subplacental vessels.

Where possible, 3 consecutive cycles of wave forms were used for analysis of the left and right uterine arteries. An attempt was made to take three consecutive and discrete readings on the right side main uterine arteries were obtained. The examinations were documented on videotapes and on hard copies.

Figure 5-2 The Picture Shows the Pattern of FHR

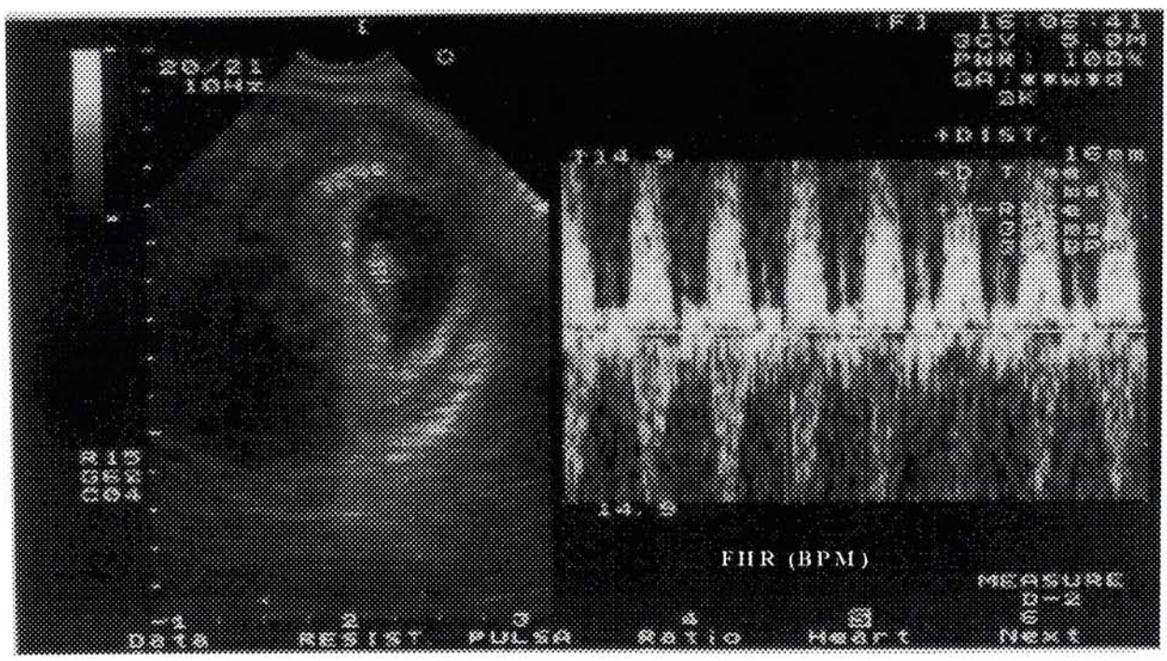
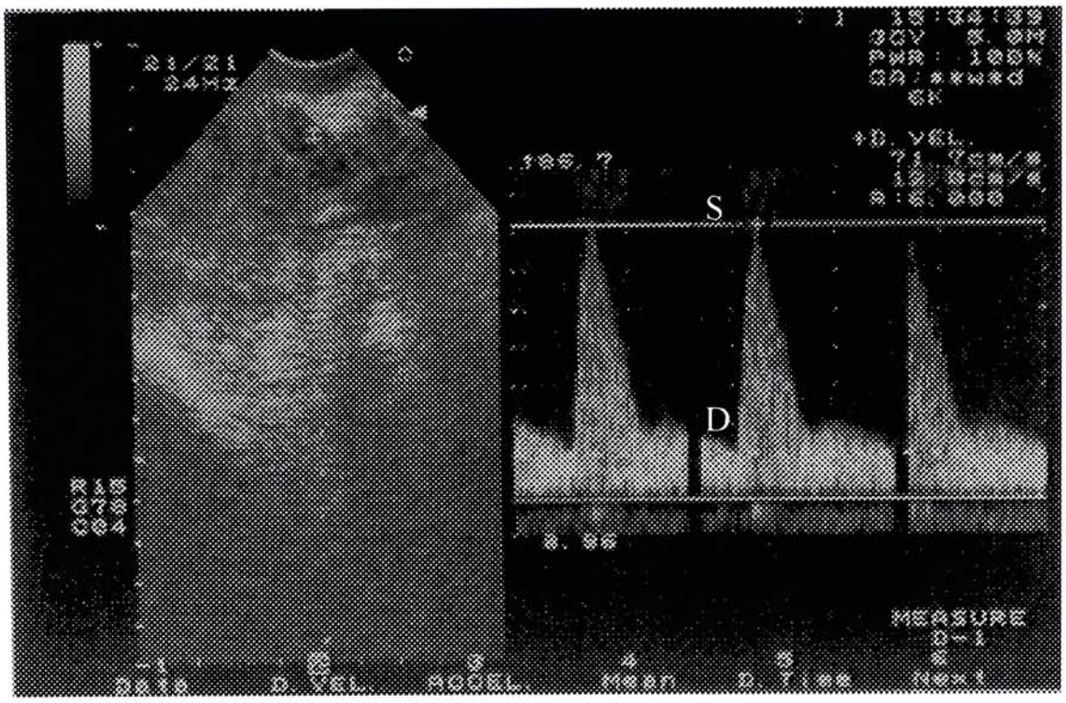


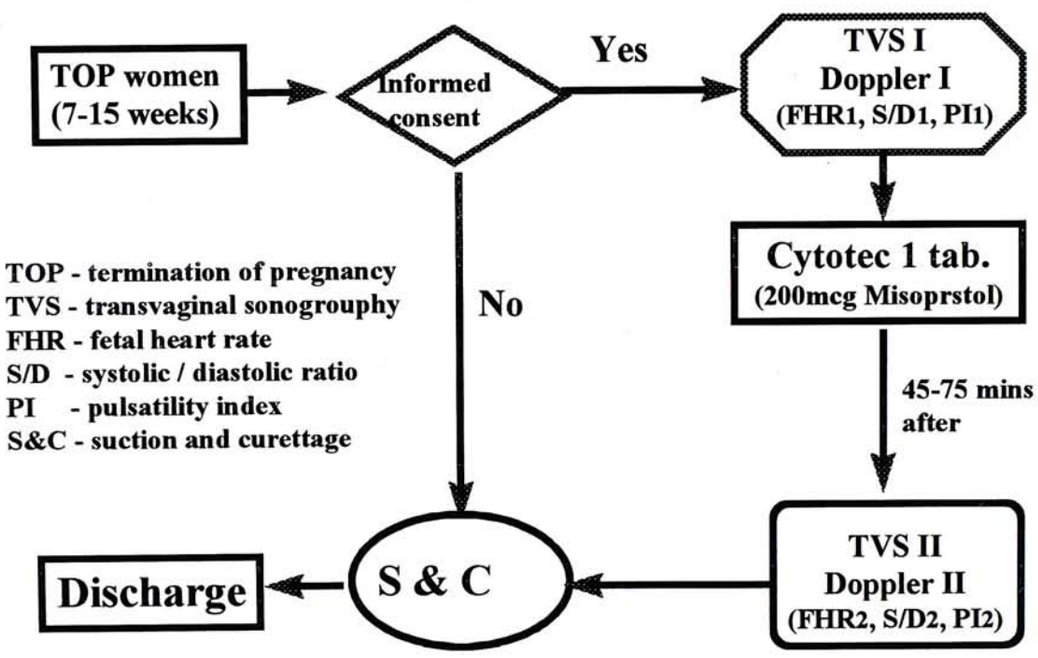
Figure 5-3 The Picture Shows the Measurement of S/D ratio



5.4.4 Misoprostol

After the first scan, each subjet was given 1 200μg tablet of misoprostol. One hour later the second scan was performed. This time the FHR, LPI, RPI, LS/D, RS/D were again measured. Furthermore, the side effect of the drug may also be recorded simultaneously. After that, the patients proceeded to TOP. Summary of the study protocol is showed below (Figure 5-6).

Figure 5-6 Summary of the Study Protocol



5.5 Data analysis

All statistical analyses were carried out on a personal computer (PC) using Statistical Package for Social Sciences - SPSS software for Windows (Version 6.0). Wilcoxon Signed-Rank Test, one of the non-parametric methods which do not require samples from normally distributed populations, was used for testing differences between before and after administration of misoprostol in whole group and all subgroups. The Mann-Whitney test was used to determine the differences between pain group and no-pain groups. P value of less than 0.05 was taken as statistically significant. A Bonferoni correction factor, which was use for making multiple (m) pairwise comparisons, 0.05/m as the confidence level for each pairwise comparison. As this study the cases were divided into three groups (whole group, pain group and no pain group), $P<0.02$ was adopted as a correction criterion for significance.

Chapter 6

Results

6. Results

6.1 The Patients' Characteristics

Forty-one pregnant women seeking termination of pregnancy (TOP) were recruited for the study. One was excluded because of asthma. Data from 40 cases were available for analysis. Both left and right UA were observed in as many subjects as possible. Thirty-seven pairs of data of both on RS/D and RPI were obtained while twenty-two and twenty-one pairs of data on LS/D and LPI were obtained respectively.

The mean age of women was 28.3 ± 8.6 years old. The mean gestational age was 10.8 ± 1.8 weeks. The mean parity was 1.5 ± 1.3. The mean of previous spontaneous abortion was 1.0 ± 0.0. The mean of TOP was 1.1 ± 0.5. Ten of them were less than 9 weeks gestation. Twenty-three were more than 9 weeks and less than or at 12 weeks gestation. Seven were at greater than 12 weeks gestation. Twelve were nulliparous and 28 were parous. The characteristics of these subjects are show in Table 6-1 below.

Table 6-1 Characteristics of Study Subjects

Characteristic	Mean	SD	Range
Age (Years)	28.3	8.6	15-42
Gestation (Weeks)	10.8	1.8	7-14
Gravida	Number	%	
1	10	25	
2	7	17.5	
>=3	23	57.5	
Parity			
0	12	30	
1	9	22.5	
2	9	22.5	
>=3	10	25	
Previous Spontaneous Abortion			
0	37	92.5	
1	3	7.5	
Previous Therapeutic TOP			
0	26	65	
1	13	32.5	
2	0	0	
>=3	1	2.5	

6.2 The Intra-observer Error

The coefficient variation of UA-S/D and UA-PI can be calculated by choosing the 'CFVAR' function, in 'Compute' variable from the 'Transform' menu on the SPSS software. The percentage of mean coefficient variations is the observer error. In this study, the same examiner conducted all measurements. Therefore the intra-observer error of UA-PI is 8.3% and UA-S/D is 11.1%.

6.3 Results of Study

6.3.1 Effect of Misoprostol on the S/D ratio of Both Uterine Arteries

As mentioned before, there were twenty-two and thirty-seven pairs of data on LS/D and RSD respectively. These were combined to total forty pairs of data on UA-S/D for analysis. The average changes between after and before UA-S/D values is 2.85(±0.57). Eight subjects showed decreasing on UA-S/D.

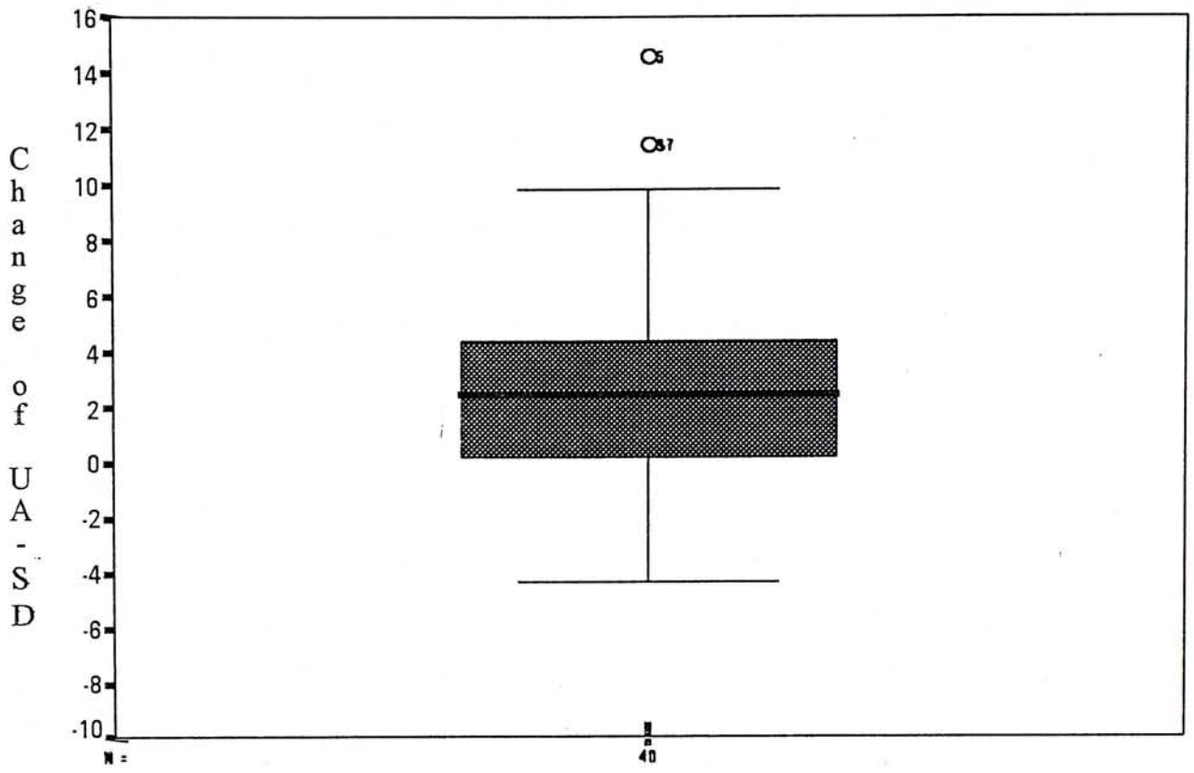
The UA-S/D increased significantly ($P<0.01$) from 6.99 (± 0.48) to 9.84 (± 0.61) after administration of misoprostol (Figure 6-1) shows the individual change of before and after in the whole group of UA-S/D. As can be seen, from first quartile to maximum of the study population, the change of UA-S/D between before and after was greater than zero. That means the study population, taken as a whole, had increase of UA-S/D after taking misoprostol. There were two probable outliers from the chart. One is 11.49 and the other is 14.69. These two

outliers may be due to the bias of the examiner. The change was statistically significant in both the group of women who had abdominal pain at the time of the second TVS (p=0.01) and those who did not have abdominal pain (p=0.01). This is summarised in Table 6-2.

Table 6-2 UA-S/D before and after Administration of misoprostol

		S/D ratio			
Groups	n	Mean (SEM), both side UA		After - Before	p value
		Before	After	Mean (SEM)	
Whole group	40	6.99 (0.48)	9.84 (0.61)	2.85 (0.57)	<0.01
Pain	22	6.50 (0.48)	8.92 (0.79)	2.42 (0.81)	0.01
No pain	18	7.58 (0.67)	10.96 (0.90)	3.38 (0.80)	0.01

Figure 6-1 UA-S/D changes before and after Misoprostol Administration



6.3.2 Effect of Misoprostol on the PI of Both Uterine Arteries

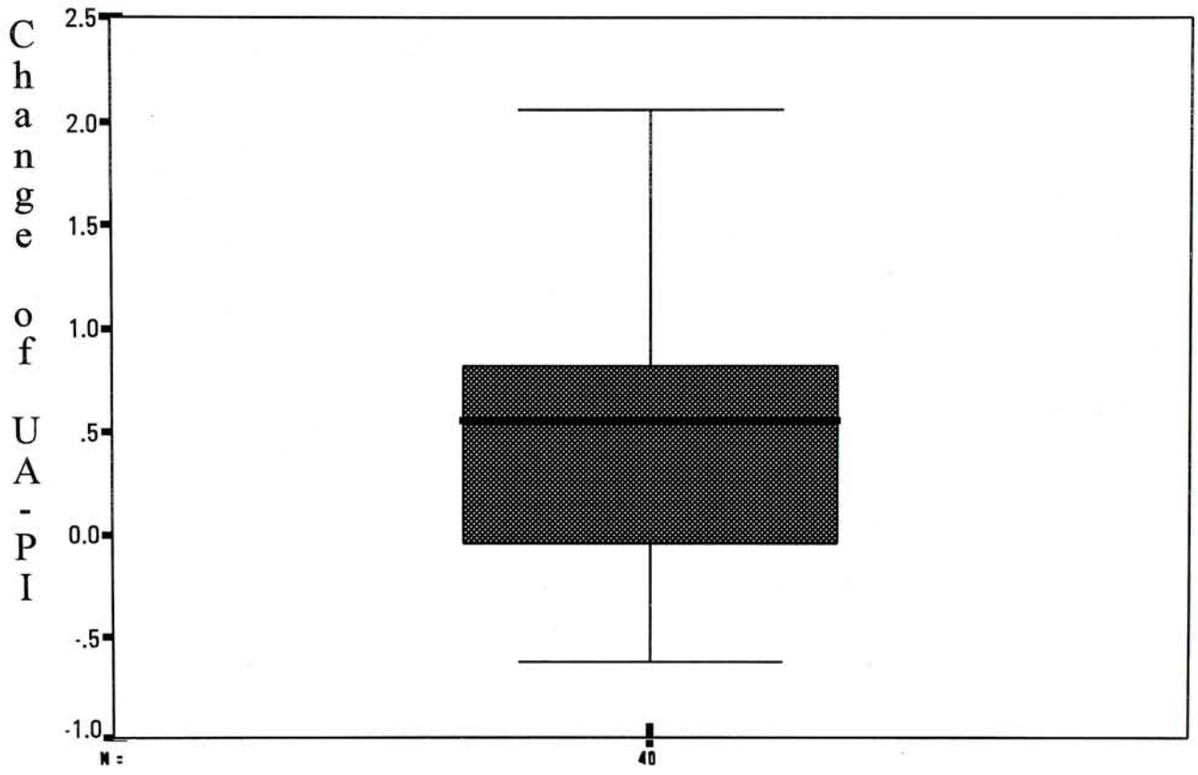
Twenty-one and thirty-seven pairs of data were collected on LPI and RPI respectively. They were combined to total forty pairs of data on UA-PI for analysis. The average changes between after and before UA-PI values is 0.46(±0.09). There were eleven pairs of cases decreasing on UA-PI.

UA-PI in both side uterine arteries also increased significantly ($P<0.01$) from 2.32 (± 0.10) to 2.78 (± 0.12) after misoprostol had been administered. Figure 6-2 shows the individual changes in the whole group of UA-PI. From the chart, from first quartile to maximum of the study population, the change of UA-PI was greater than zero. The change was statistically significant in both the group of the women who had abdominal pain at the time of the second examination ($p<0.01$) and those who did not had abdominal pain ($p<0.01$). Table 6-3 summarises the individual changes of UA-PI in the whole group and subgroups.

Table 6-3 UA-PI before and after Administration of Misoprostol

Groups	n	Pusatility index: Mean (SEM), both side UA		After - Before	p value
		Before	After	Mean (SEM)	
Whole group	40	2.32 (0.10)	2.78 (0.12)	0.46 (0.09)	<0.01
Pain	22	2.21 (0.14)	2.65 (0.14)	0.44 (0.11)	<0.01
No pain	18	2.45 (0.14)	2.93 (0.15)	0.48 (0.15)	0.01

Figure 6-2 UA-PI Changes (Bilateral) After Misoprostol



6.3.3 Effect of Misoprostol on Fetal Heart Rate (FHR)

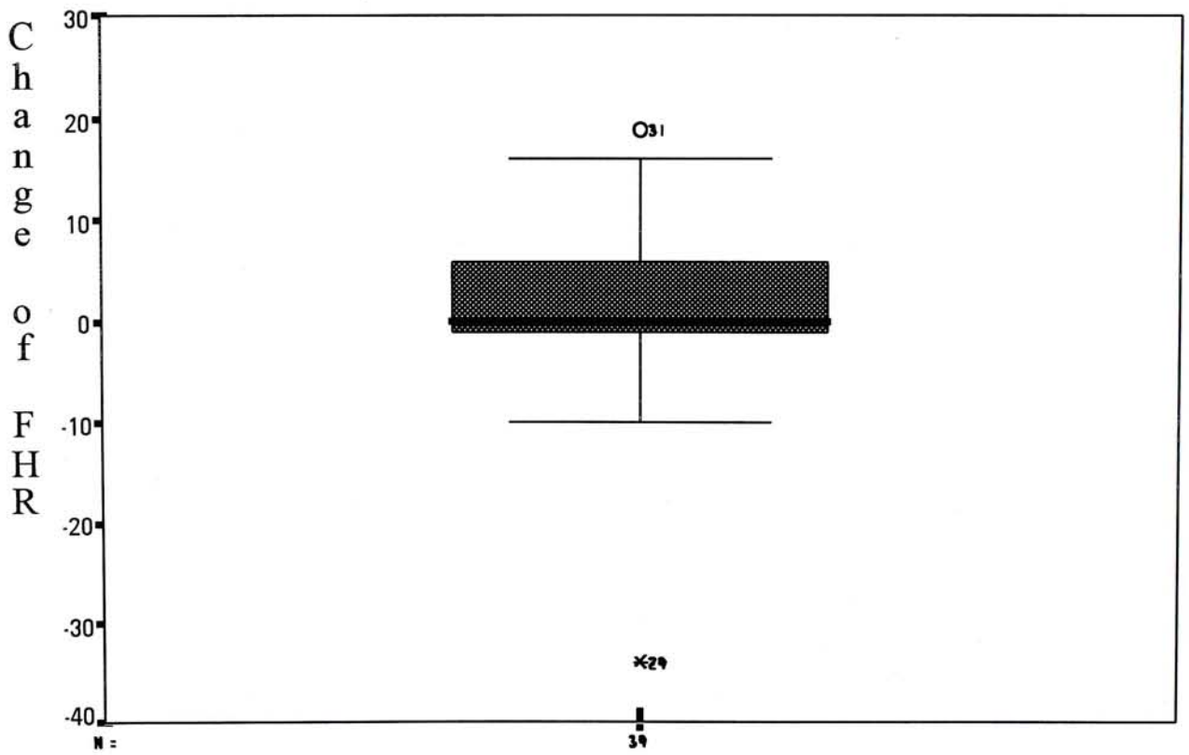
The average changes of FHR is 1.26(± 1.40). The minimum is –10 and the maximum is 16. There was a decrease seen in ten pairs of data while nineteen pairs showed an increase. However, there were no changes in ten pairs.

There were no significant changes in FHR after misoprostol ($P>0.05$). None of the fetuses died. This is shown in Table 6-4. Figure 6-3 shows the individual change of before and after FHR. There are two extremes observed value. One is possible outlier and another is probable outlier. The former had an increase of 19 bpm while the latter has decreased by 34 bpm. These two observe mothers both had no abdominal pain, no vaginal bleeding or other discomforts.

Table 6-4 Fetal Heart Rate before and after Administration of Misoprostol

Groups	n	Fetal Heart Rate Mean (SEM)		After - Before Mean (SEM)	p value
		Before	After	(bpm)	(P<0.05)
Whole group	39	169.6 (1.28)	170.8 (1.55)	1.26 (1.40)	NS

Figure 6-3 Individual FHR Changes after Misoprostol



6.3.4 Left and Right UA-S/D

Significant changes were found in the right UA-S/D in the group as a whole and in all subgroups (P all<0.01). Significant changes did not demonstrated in the left UA-S/D in the group as a whole and subgroups. This may have been due to insufficient cases. This is shown in Table 6-5and Table 6-6.

Table 6-5 Left UA-S/D before and after Administration of Misoprostol

Groups	n	Left S/D ratio Mean (SEM)		After - Before	p value
		Before	After	Mean (SEM)	
Whole group	22	7.40 (0.72)	9.21 (0.82)	1.80 (0.80)	NS(0.03)
Pain group	12	6.53 (0.92)	8.00 (1.03)	1.47 (0.96)	NS
No pain group	10	8.44 (1.10)	10.65 (1.25)	2.21 (1.39)	NS

Table 6-6 Right UA-S/D before and after Administration of Misoprostol

Groups	n	Right S/D ratio Mean (SEM)		After - Before	p value
		Before	After	Mean (SEM)	
Whole group	37	7.16 (1.09)	10.26 (0.67)	3.10 (0.58)	<0.01
Pain group	20	6.51 (0.69)	9.21 (0.85)	2.70 (0.89)	<0.01
No pain group	17	7.92 (0.87)	11.49 (1.02)	3.57(0.72)	<0.01

6.3.5 Left and Right UA-PI

The significant difference was found both in left and right UA-PI in the whole group ($P=0.02$ and $P<0.01$ respectively). However, in the subgroups, no significant changes were found in the left UA-PI whatever the women had abdominal pain or not (Table 6-7). In the right UA-PI, only pain group had significant changes, as shown in Table 6-8.

Table 6-7 Left UA-PI before and after Administration of Misoprostol

Groups	n	Left pulsatility Index Mean (SEM)		After - Before	p value
		Before	After	Mean (SEM)	
Whole group	21	2.38 (0.17)	2.70 (0.18)	0.33 (0.14)	0.02
Pain group	11	2.14 (0.27)	2.40 (0.24)	0.25 (0.21)	NS
No pain group	10	2.63 (0.19)	3.04 (0.25)	0.41 (0.19)	NS

Table 6-8 Right UA-PI before and after Administration of Misoprostol

Groups	n	Right Pulsatility Index			
		Mean (SEM)		After - Before	p value
		Before	After	Mean (SEM)	
Whole group	37	2.38 (0.11)	2.90 (0.12)	0.51 (0.11)	<0.01
Pain group	20	2.26 (0.15)	2.85 (0.18)	0.59 (0.15)	<0.01
No pain group	17	2.53 (0.16)	2.95 (0.15)	0.41 (0.18)	NS

6.3.6 The relationship Between Subgroups

There were no statistically significance almost in all parameters (UA-S/D, UA-PI, LS/D, LPI, RS/D, RPI) between pain and no pain group ($p>0.05$).

6.3.7 Side Effects of Misoprostol

Side effects of misoprostol in this study mainly were abdominal pain (n=22, 55%) and vaginal bleeding (n=16, 40%). Others included headache, nausea, vomiting, faint and dizziness. One patient had a rash (2.5%) on the back of her right hand. This is summarised in Table 6-9.

Table 6-9 Summary of Side Effects after Administration of Misoprostol

Side Effect	Number	%
Abdominal pain	22	55
Vaginal bleeding	16	40
Headaches	8	20
Nausea and vomiting	5	12.5
Faint	2	5
Dizziness	1	2.5
Rash	1	2.5

6.3.8 The Changes of UA-S/D and UA-PI According to Gestation

The S/D ratio and PI, their standard error of mean were calculated for each gestational week before and after misoprostol. Their relationships are shown in Figure 6-4 and Figure 6-5. They demonstrate that UA-S/D and UA-PI decrease as gestation increases.

Figure 6-4 Change in UA-PI with Gestation and Misoprostol

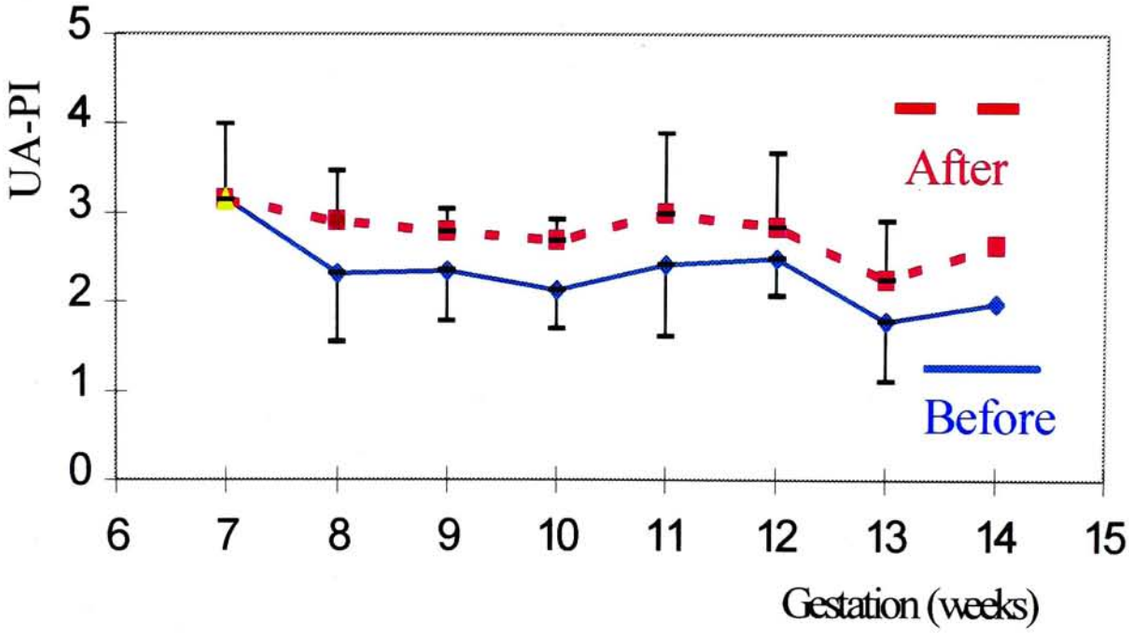
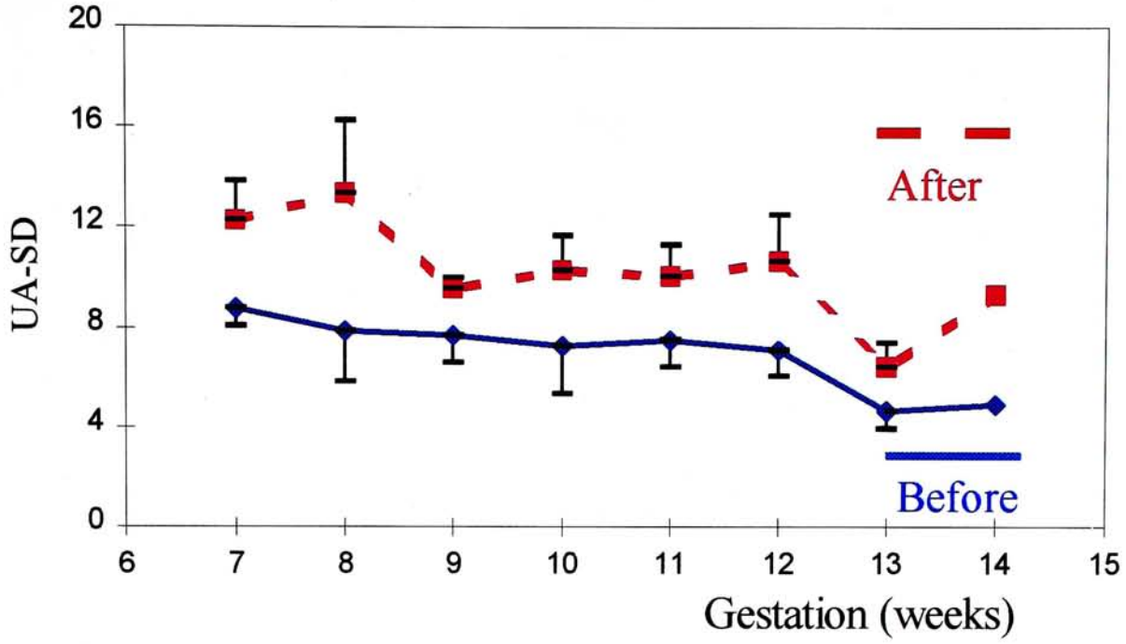


Figure 6-5 Changes in UA-S/D in Relation to Gestation



Chapter 7

Discussion

7. **Discussions and Conclusions**

7.1 Difficulties Encountered during Study

Considerable difficulty was encountered initially during the work of this thesis. The candidate has had minimal experience doing TVS and in obtaining the resistance indices required in the study. The candidate spent almost 6 months in learning to do a satisfactory TVS and obtain the data. Furthermore, obtaining consent was difficult, especially during the early part of the study. There was a general reluctance of subjects to partake in clinical experiments and in particular to undergo another TVS for purely research purpose. However, with increasing skills and experience, a satisfactory number was eventually recruited.

There was an unforeseen problem with TVS. Unlike TAS, TVS is an invasive procedure. Whilst TVS is well tolerated for routine examination, it was apparent in some women that a prolonged examination, as required in this study, was difficult to endure. Consequently, it was not possible to obtain a complete set of data in all subjects due to subjects' discomfort. Fifteen examinations had to be terminated prematurely for this reason. This problem was compounded in a few cases by difficulty identifying the left uterine artery. This means that in 19 of the possible 80 measurements, no data was available. This may have compromised the ability of the data to demonstrate the hypothesised effect. However, significant differences were nevertheless observed although it is acknowledged

that in the analysis of the subgroups, failure to demonstrate significant differences may have been the result of inadequate numbers in the subgroups.

In retrospect, the study was perhaps better done by TAS and colour Doppler. However, in the case of the colour Doppler, this equipment was not readily available for research.

Misoprostoic acid, the active metabolite of misoprostol, reaches peak plasma levels about 30-45 minutes after oral administration. Hence, the choice of 60 minutes to examine the UA flow velocity would appear to be a reasonable one.

7.2 Results of Study

Our results demonstrate a similar effect of misoprostol on the utero-placental flow velocity at the UA level to that found by Jouppila P et al. (1994) and Valentin L et al.(1995). That is: misoprostol also increases the resistance of UA in early pregnancy.

Vascular PI and S/D ratio all are angle independent and we presume that predict they reflect the resistance of vessel. Elevated PI and S/D ratio mean the resistance in these vessels was increased. Because PI reflects vascular resistance in the smaller peripheral arteries distal to the point of measurement (Maulik D et al., 1992). UA-PI can also reflect the resistance in utero-placental and myometrial arteries. There are two possibilities to explain the raised vascular resistance after treatment with misoprostol. One may be the direct PGE-like effects on the uterine

vessels that lead to vasoconstriction. Another could be the increasing uterine tonus and contractions leading to the secondary vasoconstriction in the UA. The above two investigators who studied the effect of gemeprost on UA-PI could not identify which that is the important factor. In this study, we recorded which patient has abdominal pain and which did not have abdominal pain after the administration of misoprostol. We used abdominal pain as an index of uterine contraction. Nevertheless we noted that whether there was abdominal pain or not, the UA-PI and UA-S/D increased after the treatment with misoprostol. However, pain is a poor parameter for measuring contractions. Furthermore, as we were using TVS, a prolonged examination was not acceptable to the patient. A prolonged examination may have been able to assess uterine contractions or a least change in uterine tone. Further studies involving other peripheral vessels, which are not influenced by myometrial contractions, may help to solve this question but these will not reflect the resistance of the vessels in the utero-placental circulation.

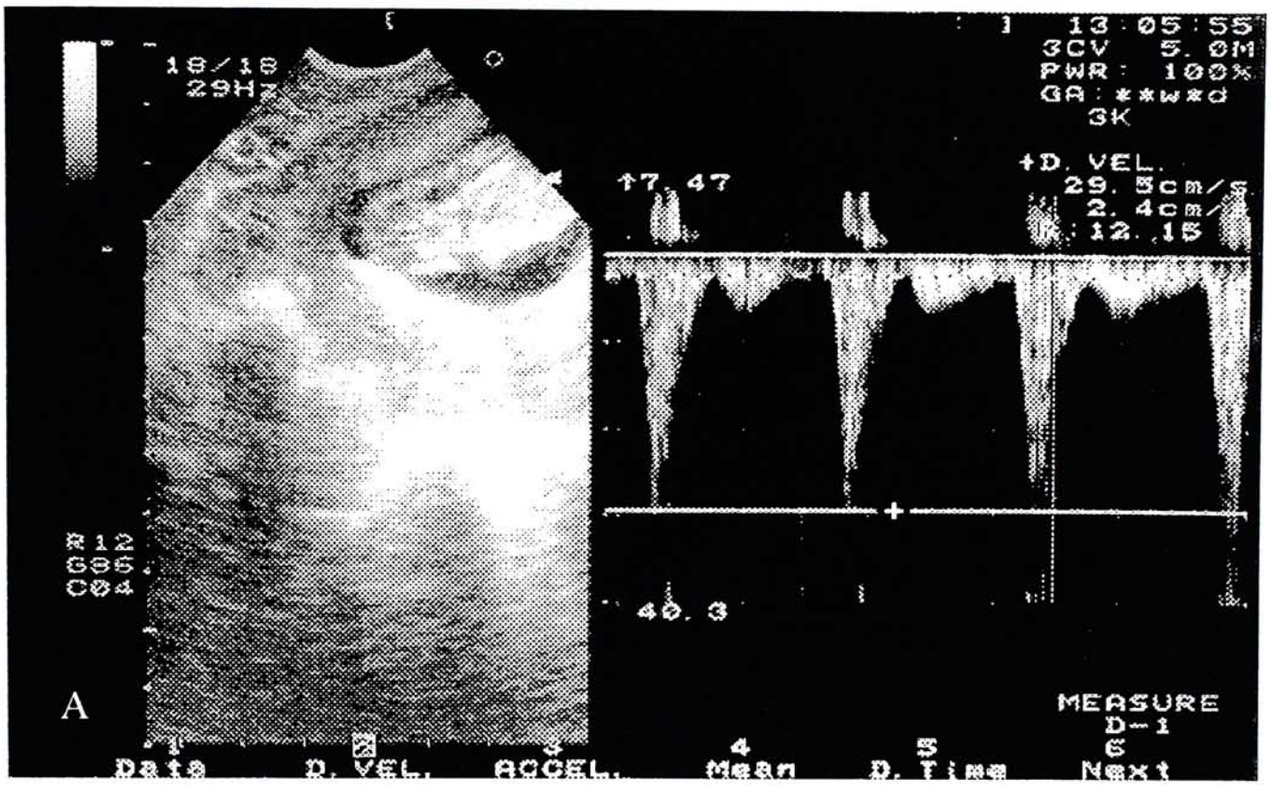
Raised UA-S/D and UA-PI may lead to decreased uterine perfusion in the utero-placental circulation. This may have resulted in a decreased blood flow to the uterus and may oxygenation of the fetus, and in extreme circumstances, causes fetal bradycardia or even fetal death (Valentin L et al., 1995). However, from the results of our research, we note that FHR was not affected by the treatment with misoprostol and all the fetuses were still alive at the second ultrasound examination. It was interesting to note that 2 of the fetuses had substantial

changes. The significance of this is unclear because episodes of profound bradycardia are not uncommonly observed during routine sonographic examination.

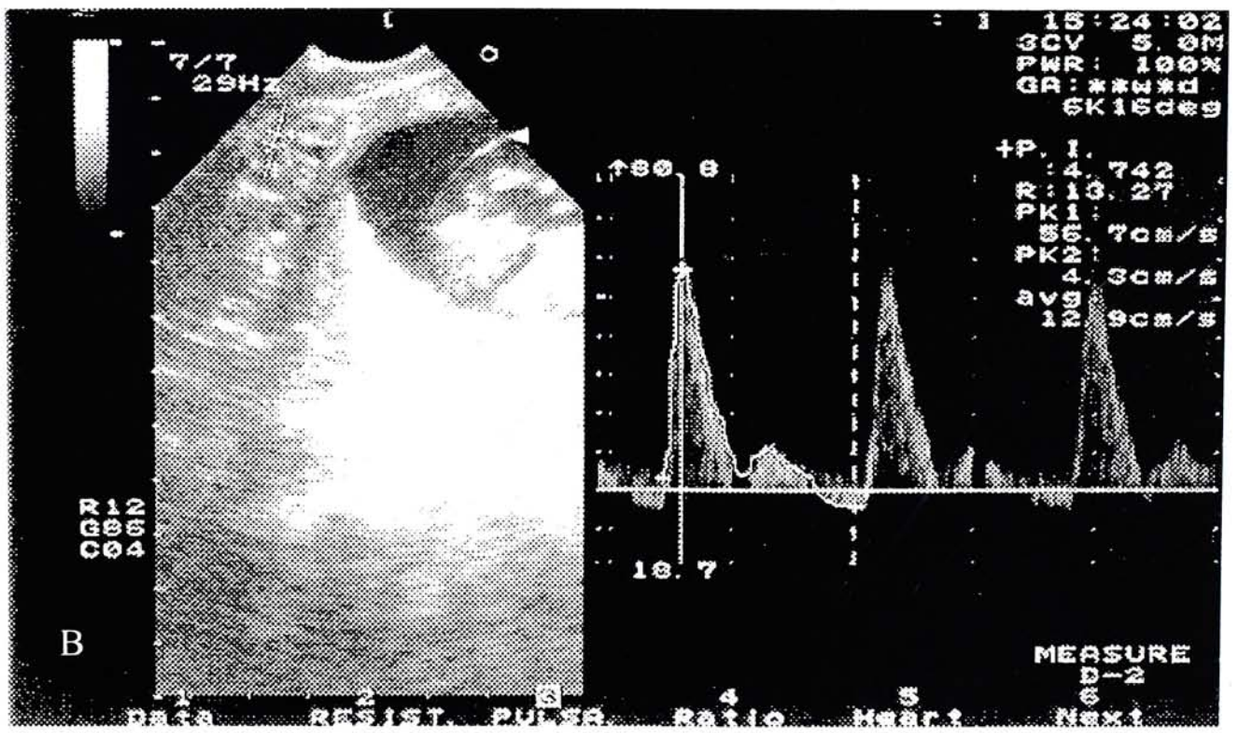
Elevation of UA-PI or UA-S/D may be due to the diastolic flow velocity decreasing after misoprostol. Valentin L et al. have studied gemeprost and measured the UA-PI over several contractions. They observed that the reversed diastolic flow velocity was usually seen 15-30 minutes after gemeprost was given and the diastolic velocities changed with uterine contractions. In our study, only one reversed diastolic flow velocities was seen. This is illustrated in below in Figure 7-1. As far as we know, there have been no studies to compare the influence of misoprostol on UA-PI by local vaginal suppositories or by oral application. When given by the oral route, the systemic side effects are greater than vaginal suppositories (Hisslein P, 1992) and the vascular effect may greater than vaginal route. However, separating them will be difficult.

The resistance indices decreased gradually as gestation increases and this is consistent with previous studies e.g., Schulman H et al., 1986). The decreasing resistance indices enable greater perfusion of the utero-placental bed and enable the mother to meet the needs of the growing fetus. However, the effect of misoprostol in this relatively narrow gestational study window is probably consistent.

Figure 7-1 Change of the Waveform after Treatment with Misoprostol



Before



After

Where the subgroup did not reach statistical significance was probably due to the small number of cases in the individual subgroups.

7.3 Implications

We have documented that even in a small dose of misoprostol has a significant effect on the resistive indices of the utero-placental circulation. In one case, there was even reversal of diastolic flow, a finding generally considered to be disadvantageous to the fetus. In late pregnancy, the uterine vascular bed may not be as sensitive to the physiological vasoconstrictor effect such as PGI_2, so the action of misoprostol in late pregnancy may be weaker than in early pregnancy.

The range of dose of misoprostol, which the fetus can tolerate, has not been found yet. Margulies M et al. (1992) have repeated one tablet which each containing 50μg through vaginal route, in a method of every 2 hours until satisfactory uterine activity was achieved, to induce labour in 33 patients and reported a 79% successful rate within 24 hours. There were few side effects on the mother and no obvious adverse effects on fetus or newborn baby. However, these studies are far too small to be able to detect changes in fetal distress and poor perinatal outcome. Further research is required into this area. The same authors have also performed a dose-finding study and found that misoprostol dose required was between 162μg and 188μg. The maximum used was 600μg, with the percentage of patients delivering within 8 hours of induction was 96% and 73% in

gestational age 28-36 or more than 36 weeks respectfully. The dosage and regimen of administration that carries the least risk for the fetus but is nevertheless effective has not been determined.

7.4 Summary of Thesis

The work of this thesis is a observational study examining the impact of the administration of 200 μgms of misoprostol on the resistive indices of the UA in early pregnancy. UA-PI and S/D ratios are simple resistance indices and independent on the angle of insonnation. This thesis also studied the influence of misoprostol on the fetal heart.

The study has shown that misoprostol can significantly increase the resistance indices including PI and S/D ratio of uterine arteries ($p<0.01$). That means the resistance of uterine arteries rose after the administration of misoprostol. In subjects who had lower abdominal pain after treatment with misoprostol, there has no difference compared with the no abdominal pain as both groups had increased UA-PI and UA-S/D. ($p<0.01$). There was no demonstrable impacts of misoprostol on the FHR overall but there were substantial changes in 2 cases.

7.5 Conclusions

Orally administered misoprostol has significant effects on the utero-placental blood flow velocity whereas it has no effects on the FHR in early pregnancy. This thesis has show that the resistance indices of the utero-placental circulation are increased after misoprostol. This means that the circulation may be affected given the same perfusion pressure. Misoprostol therefore may present a hazard for the fetus even in low doses, perhaps independently of its abortive function. Misoprostol has been used for the induction of labour where a live birth is expected. In these circumstances the possible effect of the drug on the fetus should be monitored closely in view of the documented effect on the utero-placental vascular resistance.

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ppendix I **Consent Form**

Misoprostol and Uterine Blood Flow Study

Dear Madam,

You are have a termination of Pregnancy tomorrow. As part of your care, you require transvaginal scan to confirm the gestation and to examine your adnexa. In addition, you will be given 1 tablet of misoprostol, which will make the surgical procedure easier to do because it will make your cervix softer. The drug misoprotol is a safe.

We would like to do a second vaginal scan about 1 hour after the first scan. This second is for research and is not part of your clinical management. We ask you to help in this matter because we are interested in the effect of this drug, misoprostol, on the blood flow to you uterus.

I thank you for your assistance.
Yours Sincerely

Tony Chung
Senior Lecturer
The Chinese University of Hong Kong

Consent
I,_____ understand that I shall be given 1 tablets of the drug misoprostol to assist in my operation. I also understand that the second vaginal scan is research. I give consent to both vaginal scans and the drug misoprostol.

Patient_____

Witness_____

Appendix II

有關米索前列醇與子宮血流的研究

親愛的女士:

明天妳將進行終止妊娠的手術。 作爲妳醫療服務的一部分, 妳需要作陰道超聲波檢查來確定孕齡和了解子宮附件的情況。 此外, 我們會給你一粒米索前列醇口服, 使妳的子宮頸鬆弛以利於刮宮術的進行。 這葯物是安全的。

另外, 我們想邀請妳在服葯後一小時左右接受第二次超聲波檢查, 這次檢查是作爲醫學研究用途而不屬於臨床治療的一部分。 我們需要妳的支持, 因爲我們想知道米索前列醇這種葯物對子宮血流的影響。 妳的參加與否不會影響我們對妳的服務。

多謝妳的協助。

鍾國衡

高級講師

同 意 書

我, _____明白我將會服食一粒米索前列醇來輔助我的手術, 我也明白第二次超聲波檢查是作爲醫學研究用途。 我同意服食米索前列醇和進行第二次超聲波檢查。

病人姓名:_____

病人簽署:_____

見証人姓名:_____

見証人簽署：_____

THE CHINESE UNIVERSITY
OF HONG KONG

FACULTY OF MEDICINE
SHATIN. NT. HONG KONG

香港中文大學
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TELEGRAM · SINOVERSITY TELEX · 50301 CUHK HX FAX: (852) 2603 6958

Our Reference : FM/C/13
Your Reference :

4 May 1996

Dr. Tony K.H. Chung
Dept. of Obstetrics & Gynaecology
CUHK

Dear Dr. Chung,

I write to inform you that ethical approval has been given for you to engage in the project named below:

Project Title:	**"Uterine artery blood flow and misoprostol" (ref. No. CRE-646)**
Investigator(s):	**Dr. Tony K.H. Chung, Senior Lecturer, Dept. of Obstetrics & Gynaecology, CUHK** **Ms Angel Tse On Ki, MPhil. Student, Dept. of Obstetrics & Gynaecology, CUHK**
Location of Study:	**Prince of Wales Hospital**
Duration:	**2 years**
Conditions by Clinical Research Ethics Committee (if any):	**Nil**

It will be much appreciated if the completion of the project will be reported to the Committee in due course.

Yours sincerely,

Andrew Chan
Secretary
Clinical Research Ethics Committee